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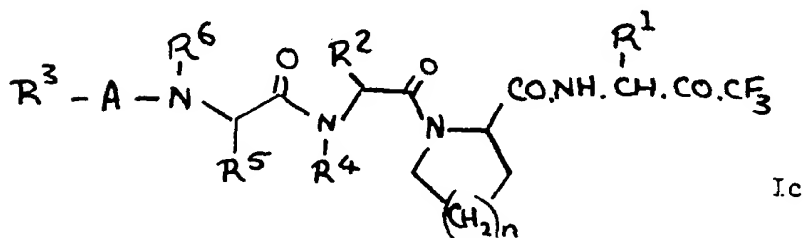
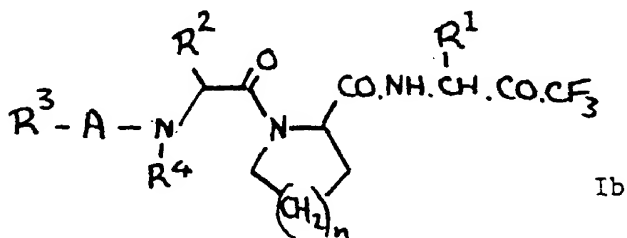
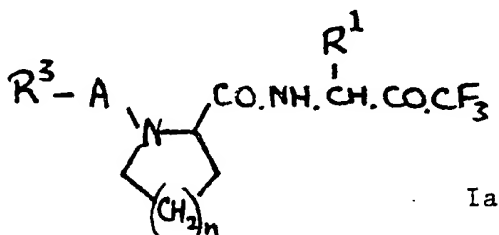
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Description

The present invention relates to certain trifluoromethyl ketone substituted peptide derivatives which are human leukocyte elastase (HLE) inhibitors making them useful whenever such inhibition is desired such as for research tools in pharmacological, diagnostic and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid arthritis and osteoarthritis in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes for preparing them, pharmaceutical compositions containing such peptide derivatives and methods for their use.

The substituted peptides of the present invention may be represented by the following formulae Ia, Ib and Ic:



wherein

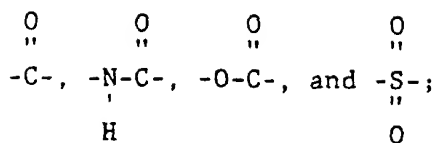
R¹ is alkyl;

R² and R⁵ are alkyl, substituted alkyl, aryl, aralkyl, substituted aralkyl or substituted aryl;

R³ is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, aralkyl, substituted aralkyl, an aliphatic heterocycle, substituted aliphatic heterocycle, an aromatic heterocycle or a substituted aromatic heterocycle;

R⁴ and R⁶ are hydrogen or methyl;

A is selected from the group consisting of



and

n is 0, 1 or 2;

and, where appropriate, the acid- and base-addition salts thereof.

Compounds of formulae Ia, Ib and Ic are referred to herein as dipeptides, tripeptides and tetrapeptides, respectively.

The compounds of the invention include those wherein

R¹ is an alkyl group containing from 1 to 5 carbon atoms, and more preferably from 2 to 5 carbons;

R² and R³ are each selected independently from the group consisting of:

(I) an alkyl group containing from 1 to 10 carbons;

(II) an alkyl group containing from 1 to 6 carbon atoms substituted by at least one member selected from the group consisting of:

(a) hydroxy;

(b) amino;

(c) alkylamino containing from 1 to 6 carbons;

(d) dialkylamino wherein each alkyl group contains from 1 to 6 carbons;

(e) alkanoyl containing from 1 to 6 carbons;

(f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;

(g) aralkanoyl containing 8 to 13 carbons;

(h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;

(i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;

(j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;

(k) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons;

(l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;

(m) arylaminocarbonyl wherein the aryl group contains 6, 10 or 12 carbons;

(n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;

(o) carboxy;

(p) aryloxy carbonyl wherein the aryl group contains 6, 10 or 12 carbons;

(q) aralkoxy carbonyl wherein the aralkoxy group contains from 7 to 13 carbons;

(r) alkanoyloxy containing from 1 to 6 carbons;

(s) aroyloxy wherein the aryl portion contains 6, 10 or 12 carbons;

(t) aralkanoyloxy containing from 8 to 14 carbons;

(u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;

(v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;

(w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons;

(x) acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamido and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

(y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 6 carbons;

(z) aralkoxycarbonylamino wherein the aralkoxy group contains from 8 to 13 carbons (e.g., benzyloxycarbonyl amino);

(aa) aryloxy carbonylamino wherein the aryloxy group contains 6, 10 or 12 carbons;

(bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 6 carbons;

(cc) aryl containing 6, 10 or 12 carbons (e.g., phenyl, biphenyl, naphthyl);

(dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members selected from the group consisting of chloro, bromo, iodo, fluoro, trifluoromethyl, hydroxy, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

(ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl).

- (ff) alkylureido wherein the alkyl group contains from 1 to 6 carbons;
- (gg) aralkylureido wherein the aralkyl group contains from 8 to 13 carbons;
- (hh) arylureido wherein the aryl group contains 6, 10 or 12 carbons; and

(iii) an aryl group of 6 carbons, e.g. phenyl.

5 R³ is selected from the group consisting of:

- (i) an alkyl group containing from 1 to 12 carbons;
- (ii) an alkyl group containing from 1 to 12 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen;
- (iii) an alkyl group containing from 1 to 12 carbons and, optionally, 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, and substituted on at least

10 one of carbon or nitrogen by 1 to 3 members selected independently from the group consisting of:

For carbon:

- (a) hydroxy, provided that it may not be on a carbon directly bonded to A;
- (b) amino, provided that it may not be on a carbon directly bonded to A;
- 15 (c) alkylamino containing from 1 to 6 carbons, provided that it may not be on a carbon directly bonded to A;
- (d) dialkylamino wherein each alkyl group contains from 1 to 6 carbons, provided that it may not be on a carbon directly bonded to A;
- (e) alkanoyl containing from 1 to 6 carbons;
- 20 (f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;
- (g) aralkanoyl containing 8 to 13 carbons;
- (h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;
- (i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;
- (j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;
- 25 (k) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons;
- (k)-(1) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a
- 30 member selected from fluoro, chloro, bromo, iodo and nitro;
- (l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;
- (l)-(1) aralkylcarbonylamino wherein the aralkyl group contains 7 to 13 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a
- 35 member selected from fluoro, chloro, bromo, iodo and nitro;
- (m) arylaminocarbonyl wherein the aryl group contains 6, 10 or 12 carbons;
- (n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;
- (o) carboxy;
- 40 (p) aryloxy carbonyl wherein the aryl group contains 6, 10 or 12 carbons;
- (q) aralkoxy carbonyl wherein the aralkoxy group contains from 7 to 13 carbons;
- (r) alkanoyloxy containing from 1 to 6 carbons;
- (s) aroyloxy wherein the aryl portion contains 6, 10 or 12 carbons;
- (t) aralkanoyloxy containing from 8 to 13 carbons;
- 45 (u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;
- (u)-(1) cycloalkylsulfonamido wherein the cycloalkyl portion contains 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);
- (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;
- (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons;
- 50 (x) acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide, and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 6 carbons;
- 55 (z) aralkoxy carbonylamino wherein the aralkoxy group contains from 8 to 13 carbons (e.g., benzyloxy carbonylamino);
- (z)-(1) aralkylaminocarbonyloxy wherein the aralkyl group contains 8 to 13 carbons;
- (z)-(2) aryloxy wherein the aryl contains 6, 10 or 12 carbons;

(z)-(3) aryloxy wherein the aryl contains 6, 10 or 12 carbons and is substituted by a member selected from aminocarbonyl, aminocarbonylalkyl where the alkyl has 1 to 3 carbons, alkoxycarbonyl having 1 to 3 carbons, and carboxy;

(aa) aryloxy-carbonylamino wherein the aryloxy group contains 6, 10 or 12 carbons;

5 (aa)-(1) arylaminocarbonyloxy wherein the aryl group contains 6, 10 or 12 carbons;

(bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 6 carbons;

(bb)-(1) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons and is optionally bonded on carbon to a carbon of an aromatic heterocyclic group as described in (gg) under R³;

10 (bb)-(2) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons substituted by an aliphatic heterocyclic group as described in (ff) under R³;

(bb)-(3) aryloxyalkylcarbonylamino wherein the aryl contains 6 or 10 carbons and the alkyl has 1 to 6 carbons;

(bb)-(4) alkylaminocarbonyloxy wherein the alkyl group contains 1 to 6 carbons;

(cc) aryl containing 6, 10 or 12 carbons (e.g., phenyl, naphthyl, biphenyl);

15 (cc)-(1) aryloxy containing 6, 10 or 12 carbons;

(dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

20 (dd)-(1) aryloxy containing 6, 10 or 12 carbons and substituted on carbon by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

(ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);

30 (ee)-(1) cycloalkyloxy containing from 3 to 15 carbons;

(ff) an aliphatic heterocyclic group of at least 4 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen (e.g., morpholine, piperazine), wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 1 to 6 carbons, an aryloxy-carbonyl group wherein the aryl group contains 6, 10 or 12 carbon atoms, an aralkyloxy-carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;

40 (ff)-(1) an aliphatic heterocyclic oxy group wherein the oxy link the is bonded directly to a carbon atom of the aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, (e.g., morpholine, piperazine), wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 1 to 6 carbons, an aryloxy-carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkyloxy-carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;

45 (gg) an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and (2) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbon atoms;

55 (gg)-(1) an aromatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon of an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and (2) from

- 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbons;
- (hh) alkylureido wherein the alkyl group contains from 1 to 6 carbon atoms;
- (hh)-(1) cycloalkylureido wherein the alkyl group contains 3 to 15 carbons;
- (ii) aralkylureido wherein the aralkyl group contains from 7 to 13 carbons;
- (ji) arylureido wherein the aryl group contains 6, 10 or 12 carbons;
- (ji)-(1) arylureido wherein the aryl group contains 6, 10 or 12 carbons and is substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- For nitrogen:
- (a) alkyl of 1 to 3 carbons;
- (b) alkanoyl containing from 2 to 6 carbon atoms;
- (c) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;
- (d) aralkanoyl containing 8 to 14 carbons;
- (e) formyl;
- (f) an aliphatic heterocyclic group wherein the amino link is bonded directly to a carbon of an aliphatic heterocyclic group defined in (ff) for the carbon substituents;
- (g) an aromatic heterocyclic group wherein the amino link is bonded directly to a carbon of the aromatic heterocyclic group defined in (gg) for the carbon substituents.
- (IV) an aryl group containing 6, 10 or 12 carbons;
- (V) an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkoxycarbonyl containing from 2 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (VI) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);
- (VI)-(1) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl), substituted by a member selected from the group consisting of carboxy and alkoxycarbonyl wherein the alkoxy group contains 1 to 4 carbons;
- (VII) an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, (e.g., morpholine, piperazine) which may be substituted at any nitrogen with a member, selected from the group consisting of an alkyl group containing from 1 to 6 carbon atoms, an alkanoyl group containing from 1 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkoxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons and an alkoxycarbonyl group containing from 2 to 7 carbons, provided that when A is OCO or NHCO then A must be bonded to a carbon atom of the aliphatic heterocyclic group;
- (VIII) an aromatic heterocyclic group containing (a) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen, and (b) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted at any carbon atom with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, and provided further that any nitrogen may be substituted by an alkyl group containing from 1 to 6 carbons, provided that when A is OCO or NHCO then A must be bonded to a carbon of the aromatic heterocycle;
- (IX) an alkenyl group of 2 to 10 carbons, having at least one double bond; and
- (X) an alkenyl group of 2 to 10 carbons, having at least one double bond and substituted by a member

selected from the group consisting of

(a) aryl of 6 or 10 carbons;

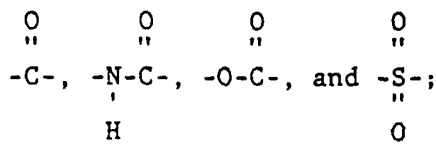
(b) aryl of 6 or 10 carbons substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and

(c) ureidocarbonyl.

R⁴ and R⁵ are independently selected from hydrogen or methyl;

n is 0, 1 or 2; and

A is selected from the group consisting of



and

where appropriate, the acid- and base-addition salts thereof.

Particular values for compounds of the invention include the following members of the groups defined above:

R¹ is an alkyl group containing 3 carbons;

R² and R⁵ are each selected independently from the group consisting of:

(I) an alkyl group containing from 1 to 4 carbons;

(II) an alkyl group containing from 1 to 4 carbons substituted by at least one member selected from the group consisting of:

(e) alkanoyl containing from 1 to 3 carbons;

(f) arylcarbonyl wherein the aryl contains 6 or 10 carbons (e.g., phenyl or naphthyl);

(g) aralkanoyl containing 8 carbons (e.g., phenylacetyl);

(h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;

(i) alkylcarbonylamino wherein the alkyl group contains from 1 to 2 carbons;

(j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 2 carbons;

(k) arylcarbonylamino wherein the aryl group contains 6 carbons (e.g., phenyl);

(l) aralkylcarbonylamino wherein the aralkyl group contains 7 carbons;

(m) arylaminocarbonyl wherein the aryl group contains 6 carbons;

(n) aralkylaminocarbonyl wherein the aralkyl group contains 7 carbons;

(o) carboxy;

(p) aryloxy carbonyl wherein the aryl group contains 6 carbons;

(q) aralkoxy carbonyl wherein the aralkoxy group contains 7 carbons;

(r) alkanoyloxy containing from 1 to 2 carbons;

(s) aroyloxy wherein the aryl portion contains 6 carbons;

(t) aralkanoyloxy containing 8 carbons;

(u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;

(v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons (e.g., 1-naphthylmethylsulfonylamino or 4-phenylbutylsulfonylamino);

(w) arylsulfonamido wherein the aryl group contains 6 or 10 carbons;

(x) acylsulfonamido containing 1 to 15 carbons (e.g. phenylsulfonylaminocarbonyl);

(y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 2 carbons;

(z) aralkoxy carbonylamino wherein the aralkoxy group contains 7 carbons (e.g., benzyloxycarbonylamino);

(aa) aryloxy carbonylamino wherein the aryloxy group contains 6 carbons;

(bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 3 carbons;

(cc) aryl containing 6 or 10 carbons (e.g., phenyl or naphthyl);

(dd) aryl containing 6 or 10 carbons and substituted by 1 to 3 members selected from the group consisting of chloro, bromo, iodo, fluoro, trifluoromethyl, hydroxy, alkyl (1 to 2 carbons), alkoxy (1 to 2

carbons), alkoxycarbonyl (2 to 3 carbons), carboxy, 5-tetrazolo and acylsulfonamido (1 to 15 carbons);
(ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl).

(ff) alkylureido wherein the alkyl group contains from 1 to 2 carbons;

(gg) aralkylureido wherein the aralkyl group contains 7 carbons;

5 (hh) arylureido wherein the aryl group contains 6 or 10 carbons; and

(III) an aryl group of 6 carbons.

R³ is selected from the group consisting of:

(I) an alkyl group containing from 1 to 12 carbons;

10 (II) an alkyl group containing from 1 to 12 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen;

(III) an alkyl group containing from 1 to 12 carbons and, optionally, 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, and substituted on at least one of carbon or nitrogen by 1 to 3 members selected independently from the group consisting of:

For carbon:

15 (e) alkanoyl containing from 1 to 6 carbons;

(f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;

(g) aralkanoyl containing 8 to 13 carbons;

(h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;

(i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;

20 (j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;

(k) arylcarbonylamino wherein the aryl group contains 6 or 10 carbons;

(k)-(1) arylcarbonylamino wherein the aryl group contains 6 or 10 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido containing 1 to 15 carbons;

25 (l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;

(l)-(1) aralkylcarbonylamino wherein the aralkyl group contains 7 to 13 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido containing 1 to 15 carbons;

(m) arylaminocarbonyl wherein the aryl group contains 6 or 10 carbons;

30 (n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;

(o) carboxy;

(p) aryloxy carbonyl wherein the aryl group contains 6 or 10 carbons;

(q) aralkoxy carbonyl wherein the aralkoxy group contains from 7 to 13 carbons;

(r) alkanoyloxy containing from 2 to 3 carbons;

35 (s) aroyloxy wherein the aryl portion contains 6 or 10 carbons;

(t) aralkanoyloxy containing from 8 to 13 carbons;

(u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;

(u)-(1) cycloalkylsulfonamido wherein the cycloalkyl portion contains 3 to 15 carbons (e.g., the cycloalkyl may be cyclohexyl, adamantyl, norbornyl), e.g., 1-adamantylsulfonamido;

40 (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;

(w) arylsulfonamido wherein the aryl group contains 6 or 10 carbons;

(x) acylsulfonamido containing 1 to 15 carbons;

(y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 3 carbons;

45 (z) aralkoxy carbonylamino wherein the aralkoxy group contains from 8 to 13 carbons (e.g., benzyloxy carbonylamino);

(z)-(1) aralkylaminocarbonyloxy wherein the aralkyl group contains 7 to 13 carbons;

(z)-(2) aryloxy wherein the aryl contains 6, 10 or 12 carbons;

(z)-(3) aryloxy wherein the aryl contains 6, 10 or 12 carbons and is substituted by a member selected from aminocarbonyl, aminocarbonylalkyl where the alkyl has 1 to 3 carbons, alkoxycarbonyl having 2 to 4 carbons, and carboxy;

50 (aa) aryloxy carbonylamino wherein the aryloxy group contains 6 or 10 carbons;

(aa)-(1) arylaminocarbonyloxy wherein the aryl group contains 6 or 10 carbons;

(bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 6 carbons;

55 (bb)-(1) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons and is optionally bonded to a carbon of an aromatic heterocyclic group as described in (gg) under R³;

(bb)-(2) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons substituted by an aliphatic heterocyclic group as described in (ff) under R³;

(bb)-(3) aryloxyalkylcarbonylamino wherein the aryl contains 6 or 10 carbons and the alkyl has 1 to 6

carbons;

(bb)-(4) alkylaminocarbonyloxy wherein the alkyl group contains 1 to 6 carbons;

(cc) aryl containing 6 or 10 carbons (e.g., phenyl or naphthyl);

(cc)-(1) aryloxy containing 6 or 10 carbons;

5 (dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (1 to 15 carbons);

10 (dd)-(1) aryloxy containing 6, 10 or 12 carbons and substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, acylsulfonamido (1 to 15 carbons), aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl and 5-tetrazolo;

(ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl or norbornyl);

(ee)-(1) cycloalkyloxy containing from 3 to 15 carbons;

15 (ff) an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen (e.g., morpholine, piperazine), wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 2 to 6 carbons, an
20 aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkyloxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;

(ff)-(1) an aliphatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon of an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero
25 atoms each of which is selected independently from the group consisting of nitrogen and oxygen, wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 2 to 6 carbons, an aryloxy carbonyl group wherein the aryl
30 group contains 6, 10 or 12 carbons, an aralkyloxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons (e.g., morpholine, piperazine);

(gg) an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and
35 (2) from 1 to 2 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing methyl, alkoxy containing from 1 to 2 carbons, alkanoyl containing from 2 to 3 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbons;

40 (gg)-(1) an aromatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon atom of an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and
45 (2) from 1 to 2 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, alkoxy containing from 1 to 2 carbons, alkanoyl containing from 2 to 3 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbons;

(hh) alkylureido wherein the alkyl group contains from 1 to 6 carbons;

50 (hh)-(1) cycloalkylureido wherein the alkyl group contains 3 to 15 carbons;

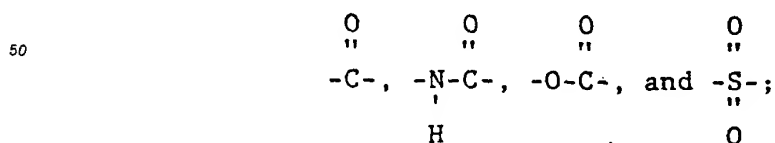
(ii) aralkylureido wherein the aralkyl group contains from 7 to 13 carbons;

(jj) arylureido wherein the aryl group contains 6 or 10 carbons;

55 (jj)-(1) arylureido wherein the aryl group contains 6 or 10 carbons and is substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, acylsulfonamido (1 to 15 carbons), aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl and 5-tetrazolo;

For nitrogen:

- (a) alkyl of 1 to 3 carbons;
 (b) alkanoyl containing from 2 to 6 carbons;
 (c) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;
 (d) aralkanoyl containing 8 to 13 carbons;
 5 (e) formyl;
 (f) an aliphatic heterocyclic amino group wherein the amino link is bonded directly to a carbon of an aliphatic heterocyclic group defined in (ff) for the carbon substituents;
 (g) an aromatic heterocyclic amino group wherein the amino link is bonded directly to a carbon of the aromatic heterocyclic group defined in (gg) for the carbon substituents.
- 10 (IV) an aryl group containing 6 or 10 carbons;
 (V) an aryl group containing 6 or 10 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkoxycarbonyl containing from 2 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and
 15 acylsulfonamido containing from 1 to 15 carbons (e.g., 4-[(4-chlorophenyl)sulfonylamino]carbonyl]-phenyl or 4-[(4-bromophenyl)sulfonylamino]carbonyl]phenyl);
 (VI) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl or norbornyl);
 (VI)-(1) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl or norbornyl), substituted by a member selected from the group consisting of carbon and alkoxycarbonyl wherein the
 20 alkoxy group contains 1 to 4 carbons;
 (VII) an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of nitrogen and oxygen, (e.g., morpholine, piperazine), which may be substituted at any nitrogen with a member selected from the group consisting of methyl, an alkanoyl group containing from 2 to 6 carbons, an aryloxycarbonyl
 25 group wherein the aryl group contains 6 or 10 carbons, an aralkoxycarbonyl group wherein the aralkyl group contains 7 carbons and an alkoxycarbonyl group containing from 2 to 3 carbons, provided that when A is OCO or NHCO, then A must be bonded to a carbon of the aliphatic heterocyclic group;
 (VIII) an aromatic heterocyclic group containing (a) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen, and
 30 (b) from 1 to 2 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted at any carbon atom with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, alkoxy containing from 1 to 2 carbons, alkanoyl containing from 2 to 3 carbons, carboxy, and provided further that any nitrogen may be substituted by an alkyl group containing from 1 to 6 carbons, provided that when A is OCO or NHCO
 35 then A must be bonded to a carbon of the aromatic heterocycle;
 (IX) an alkenyl group of 2 to 10 carbons, having at least one double bond;
 (X) an alkenyl group of 2 to 10 carbons, having at least one double bond and substituted by a member selected from the group consisting of
 40 (a) aryl of 6 or 10 carbons;
 (b) aryl of 6 or 10 carbons substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, acylsulfonamido (1 to 15 carbons) and 5-tetrazolo; and
 (c) ureidocarbonyl.
- 45 R⁴ and R⁵ are each hydrogen;
 n = 1; and
 A is selected from the group consisting of



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More particular values include:
 R¹ selected to be isopropyl;
 R² selected from the group consisting of:

- (l) an alkyl group containing 2 to 3 carbons;
- (ll)(q) ethyl substituted by aralkoxycarbonyl wherein the aralkoxy group contains 7 carbons;
- (w) butyl substituted by an arylsulfonamido wherein the aryl portion has 6 carbons;
- (x) ethyl substituted by acylsulfonamido containing 7 carbons (e.g., 2-(phenylsulfonaminocarbonyl)-ethyl);
- (z) butyl substituted by aralkyloxycarbonylamino wherein the aralkoxy portion contains 7 carbons, (e.g., benzyloxycarbonylamino);
- (cc) methyl substituted by an aryl containing 6 carbons; and
- (III) aryl containing 6 carbons.
- R³ selected from the group consisting of:
- (I) branched alkyl containing 4 carbons;
- (II) an alkyl group containing 5 carbons and 2 oxygens;
- (III)(k) ethyl substituted by arylcarbonylamino wherein the aryl portion contains 6 carbons;
- (l) ethyl substituted by an aralkylcarbonylamino wherein the aralkyl portion contains 13 carbons;
- (n) ethyl substituted by aralkylaminocarbonyl wherein the alkyl contains 7 carbons;
- (o) an alkyl group containing 2 or 10 carbons and substituted by carboxy;
- (w) an alkyl group containing 5 carbons and substituted by arylsulfonamido wherein the aryl portion contains 6 carbons;
- (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonaminocarbonyl)ethyl, 2-(phenylsulfonaminocarbonyl)ethyl, 2-[(1-adamantyl)sulfonaminocarbonyl]ethyl, and 2-[(1-naphthyl)sulfonaminocarbonyl]ethyl;
- (y) an alkyl group containing 2 or 10 carbons and substituted by methoxycarbonyl;
- (z) an alkyl group containing 2 to 5 carbons and substituted by aralkoxycarbonyl wherein the aralkoxy portion contains 7 carbons;
- (aa) an alkyl containing 5 carbons and substituted by aryloxycarbonylamino wherein the aryloxy portion contains 6 carbons;
- (bb) ethyl substituted by alkoxycarbonylamino wherein the alkyl group contains 4 carbons; and an alkyl containing 5 carbons and substituted by an alkyloxycarbonylamino wherein the alkoxy group contains 2 carbons and is substituted on the terminal carbon via a direct link to a carbon atom of an aromatic heterocycle containing 5 carbons and 1 nitrogen;
- (bb)-(3) a propyl group substituted by an aryloxyalkylcarbonylamino wherein the aryl group contains 6 carbons and the alkyl group is methyl;
- (cc) methyl or butyl substituted by aryl containing 6 carbons; and a branched alkyl group containing 5 carbons and substituted by 2 aryl groups each containing 6 carbons;
- (dd) a member selected from the group consisting of an alkyl containing 1 or 2 carbons and substituted with an aryl containing 6 carbons wherein the aryl is further substituted by carboxy; methyl substituted by an aryl containing 6 carbons wherein the aryl is further substituted by methoxycarbonyl; ethyl substituted by an aryl containing 6 carbons wherein the aryl is further substituted by ethoxycarbonyl; and ethyl substituted by an aryl containing 6 carbons wherein the aryl is further substituted by an acylsulfonamido containing 7 carbons;
- (ee) ethyl substituted by a cycloalkyl containing 10 carbons, (e.g., 1-adamantylethyl);
- (ff) ethyl substituted by an aliphatic heterocycle containing 4 carbons, 1 nitrogen and 1 oxygen (e.g., 2-(4-morpholinyl)ethyl);
- (gg) an alkyl containing 1 to 2 carbons and substituted by an aromatic heterocycle containing 4 carbons and 1 sulfur (e.g., (2-thiophenyl)methyl or 2-(3-thiophenyl)ethyl); and ethyl substituted by an aromatic heterocycle containing 5 carbons and 1 nitrogen;
- (jj)-(1) an alkyl group containing 5 carbons and substituted by an arylureido wherein the aryl portion contains 6 carbons and wherein the aryl portion is further substituted by ethoxycarbonyl or carboxy;
- (zz) propyl substituted by aryloxy wherein the aryl contains 6 carbons; a branched alkyl group containing 5 carbons and substituted by 2 aryloxy groups each containing 6 carbons;
- (zzz) methyl or propyl substituted by an aryloxy containing 6 carbons wherein the aryloxy is further substituted by aminocarbonyl; and methyl substituted by an aryloxy containing 6 carbons wherein the aryloxy is further substituted by ethoxycarbonyl;
- (IV) an aryl group containing 6 or 10 carbons, e.g., phenyl or naphthyl;
- (V) an aryl group containing 6 carbons substituted by a member selected from the group consisting of fluoro, hydroxy, carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbonylamino, an acylsulfonamido containing 2 carbons, (e.g., 4-(methylsulfonaminocarbonyl)phenyl), an acylsulfonamido containing 7 carbons (e.g., 4-(phenylsulfonaminocarbonyl)phenyl, 4-[(4-chlorophenyl)-

sulfonylaminocarbonyl]phenyl, or [(4-bromophenyl)sulfonylaminocarbonyl]phenyl), an acylsulfonamido containing 11 carbons (e.g., 4-(1-naphthylsulfonylaminocarbonyl]phenyl), an acylsulfonamido containing 14 carbons (e.g., 4-(4-bromophenylsulfonylamino(benzyl)carbonyl]phenyl); an aryl group containing 6 carbons and substituted by 2 chloros; and an aryl group containing 6 carbons and substituted by one chloro

5 and one amino;

(VI) a cycloalkyl containing 10 carbons (e.g., 1-adamantyl);

(VI)-(1) a cycloalkyl containing 5 carbons and substituted by carboxy or ethoxycarbonyl; and

(X) an alkenyl group containing 2 carbons and substituted by a member selected from the group consisting of carboxy, carboxyphenyl (e.g., E-4-carboxyphenyl), ethoxycarbonyl, ureidocarbonyl (e.g., Z-

10 (3-aminocarbonylamino-3-oxo-1-propenyl), acylsulfonamido (e.g., 4-[(4-chlorophenyl)-sulfonylaminocarbonyl]phenyl), and 4-carboxyphenyl (e.g., E-2-(4-carboxyphenyl)ethenyl.

R⁴ selected as hydrogen;

R⁵ selected from the group consisting of:

(I) n-butyl;

15 (II)(q) ethyl substituted by aralkoxycarbonyl wherein the aralkoxy contains 7 carbons; and

(II)(z) butyl substituted by aralkyloxycarbonylamino wherein the aralkyl group contains 7 carbons;

A is as defined above; and

n = 1.

The following provisos apply to the compounds of this invention:

20 (1) alkyls may be straight or branched chain;

(2) no carbon of an alkyl may be directly bonded to two heteroatoms;

(3) no heteroatom may be directly bonded to a sulfur, nitrogen or oxygen; and

(4) alkenyls of IX and X for R³ may not be 1,1-disubstituted, and a carbon of a double bond may not be directly bonded to an oxygen or nitrogen.

25 The salts of the compounds of formulae Ia, Ib and Ic include pharmaceutically-acceptable base- or acid-addition salts such as those made with a mineral acid, e.g., hydrochloric, or an organic acid such as citric, maleic, fumaric or acetic. Base-addition salts include those made with alkali metal hydroxides such as sodium hydroxide, alkali metal carbonates and bicarbonates, alkaline earth hydroxides and organic amine salts. Such salts may be prepared by dissolving the peptide derivative in a mixture of water and a water-

30 miscible organic solvent, adding an aqueous solution of the base and recovering the salt from the aqueous solution.

The preferred compounds of the present invention are of the S configuration (i.e., that of the naturally occurring L-amino acids) at chiral centers identified by * in formulae IIa, IIb, and IIc below. The methods of synthesis described below in Methods A and B provide a diastereomeric mixture as a result of the presence

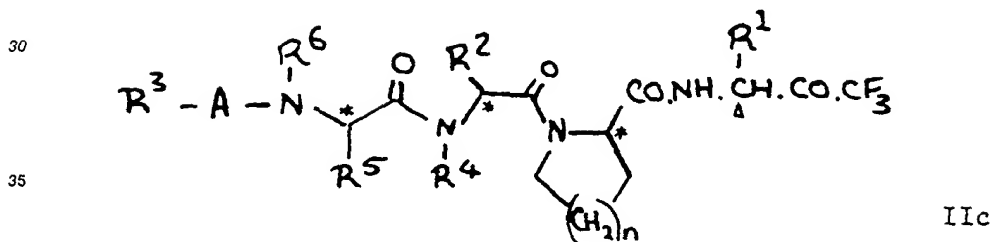
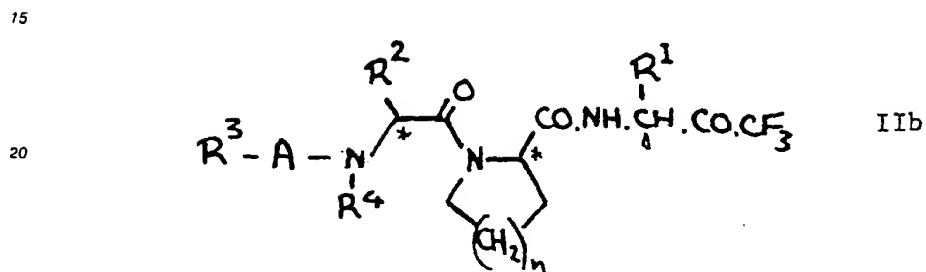
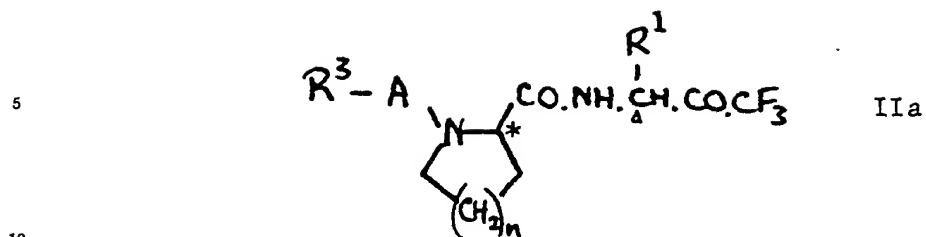
35 of the products with both the R and the S configurations at the chiral center identified by the symbol Δ. The methods of separation and synthesis described below in Methods C and D provide compounds which are substantially enantiomerically and diastereomerically pure. The preferred compounds are those assigned the S configuration at the center identified by the symbol Δ.

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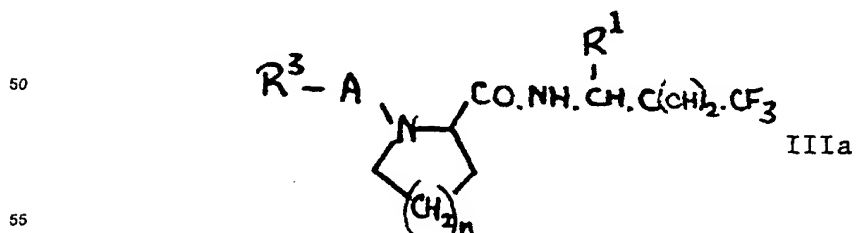
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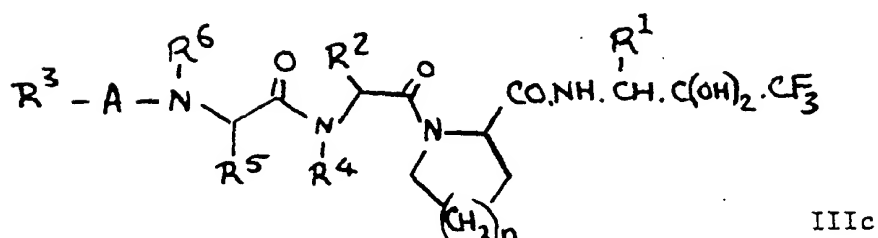
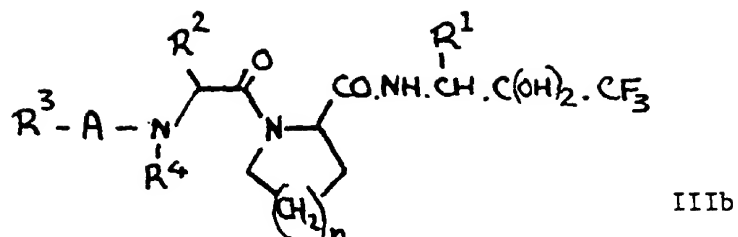


As will be appreciated by those skilled in the art, the activity of the individual isomers is not the same and, it is therefore preferred to utilize the more active isomer. The present invention includes both the diastereomeric mixture and the active S and R isomers.

As will be appreciated by those skilled in the art, the trifluoromethyl ketones can exist as solvates, particularly hydrates, represented by formulae IIIa, IIb and IIc, and these are encompassed by the present invention.

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It is preferred to prepare the peptide derivatives of the present invention from commercially available alpha amino acids (i.e., those in which the NH₂ group is attached to the carbon atom next to the -COOH group). Because of this the preferred R² and R⁵ substituents in the above formulae for tri- and tetrapeptide derivatives are those obtained from one of the following amino acids: alanine, valine, norvaline, leucine, isoleucine, norleucine, phenylalanine, tryptophan, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, threonine, serine, α-aminobutyric acid, and phenylglycine.

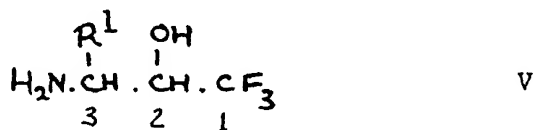
Preferred groups of compounds include those listed as the main title for each of Examples 6, 11, 15-18, 20-28, 51-56, 58, 59, 62, 63, 65, 68, 71, 72, 74, 75, 77-79, 82, 84-91, 93-111, 114, 115, 117, 119 and 121-126. Of these the ones for Examples 16, 24, 27, 52, 58, 71, 74, 77-79, 85, 89, 93-96, 98, 100, 104-107, 110, 114, 115, 119 and 123-125 are more preferred and those of Examples 77, 95, 104, 114 and 115 are the most preferred.

According to a further feature of the invention there are provided pharmaceutical compositions comprising a pharmaceutically-effective amount of at least one peptide derivative of formulae Ia, Ib or Ic and a pharmaceutically-acceptable diluent or carrier.

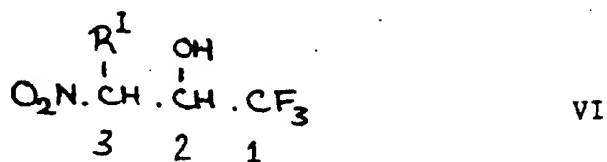
The compounds of formulae Ia, Ib and Ic can be prepared as follows:

Method A

Stage 1 is the preparation of the aminoalcohol V

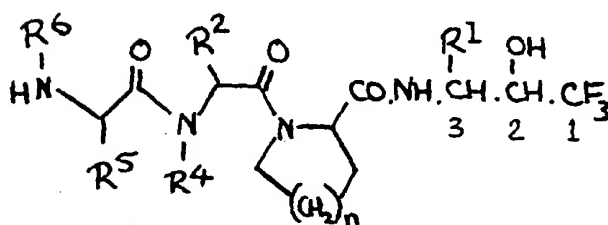
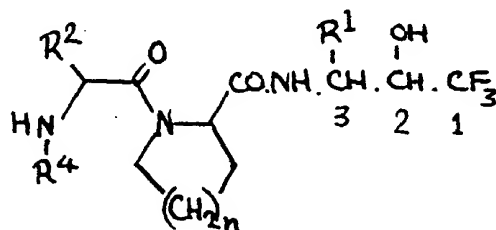
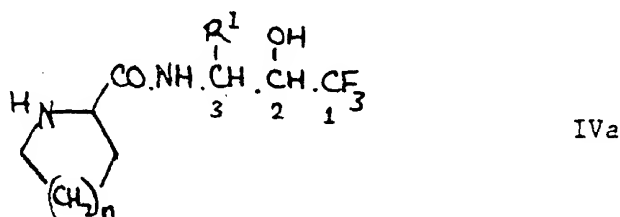


(conveniently isolated as the hydrochloride salt). Henry condensation (McBee, E. T., et al, J. Amer. Chem. Soc., 78:4053 (1956)) of an appropriate nitroalkane of formula R¹CH₂NO₂ (prepared by standard methods if not otherwise available) with trifluoroacetaldehyde ethyl hemiacetal of formula [CF₃CH(OH)OCH₂CH₃] provides a nitroalcohol of formula VI:



10 which is obtained as a mixture of two racemic diastereomers ([2(RS),3(RS)] and [2(RS),3(SR)]). (For example, see Example 1b.) Reduction of the nitro group in compound VI with an appropriate reducing agent affords compound V as a mixture of two racemic diastereomers ([2(RS),3(RS)] and [2(RS),3(SR)]). (For example, see Example 1c.) This amine salt is used directly for further synthesis.

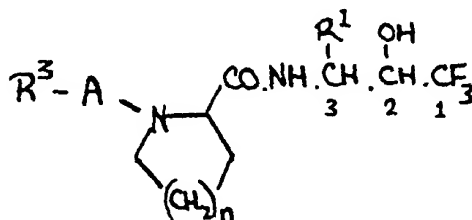
Stage 2 is the conversion of compound V into key intermediates of formulae IVa, and IVb and IVc



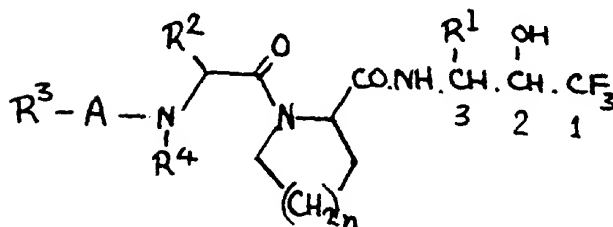
55 using methods commonly known to those skilled in the art, such as those described in M. Bodanszky, Principles of Peptide Synthesis, Springer-Verlag, Berlin, (1984), and The Peptides. Analysis, Synthesis and Biology (ed. E. Gross of J. Meienhofer), Vols. 1-5, (Academic Press, New York) 1979-1983. Use of appropriately N-protected cyclic amino acids (such as CBZ-proline), followed by peptide coupling procedures and appropriate amino deprotection affords compounds of formula IVa. Similar coupling with

appropriate N-protected dipeptide acids and tripeptide acids and deprotection affords compounds of formulae IVb and IVc, respectively. In addition, compounds of formula IVa can be converted into compounds of IVb or IVc by utilizing the same peptide methodology. The products obtained as here described are mixtures ([2(RS), 3(RS)] and [2(RS),3(SR)]) unless a separation is carried out.

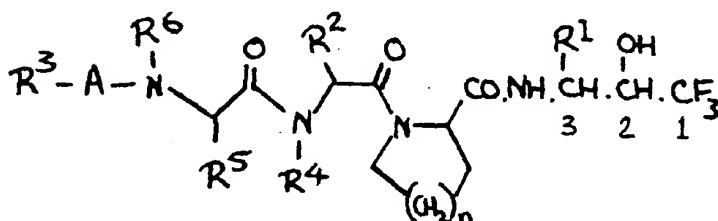
5 Stage 3 is the conversion of intermediates of compounds IVa, IVb, or IVc into intermediates VIIa, VIIb, VIIc:



VIIa



VIIb



VIIc

45 by their reaction with appropriate reagents for the formation of amides, ureas, urethanes, and sulfonamides including acid chlorides, anhydrides, mixed anhydrides, isocyanates, carbonates such as 4-nitrophenyl carbonates (prepared as described in Kunz, H. et al., Angew. Chem. Int. Ed. (Eng), 22, 783-784 (1983)), chloroformates, sulfonyl chlorides, and sulfinyl chlorides, followed by oxidation by methods well known in the literature. The products obtained as here described are mixtures ([2(RS),3(SR)] and [2(RS),3(RS)]) unless a separation is carried out.

As will be clear to one skilled in the art, the order of steps in Stage 2 and 3 may be altered if appropriate considerations relative to coupling methods, racemization, deprotection methods, etc. are followed. Thus, under appropriate conditions intermediates of formula VIIa may also be prepared directly from compounds of formula V; intermediates of formula VIIb may also be prepared directly from compounds of V, IVa, or IVb.

55 Stage 4 is the oxidation of intermediates of formulae VIIa, VIIb or VIIc to provide products Ia, Ib or Ic,

respectively. Methods which are useful include the use of oxalylchloride, DMSO and a tertiary amine (see Marx, M. et al., J. Org. Chem., 49, 788-793 (1984) with the best results being obtained with 10-20 equivalents of oxidizing agent), the use of acetic anhydride and DMSO, the use of chromium trioxide pyridine complex in methylene chloride, and the use of Dess-Martin periodinane [1,1,1-triacetoxy-2,1-benzoxiodol-3(3H)-one] (method of Dess, D. B. et al, J. Org. Chem., 48, 4155-56 (1983)). The preferred method is the use of Dess-Martin periodinane. Unless they have been separated, the products Ia, Ib and Ic obtained by this method will contain a mixture [3(RS)] which will consist substantially of two diastereomers if the centers corresponding to those indicated with an * in formulae IIa, IIb, and IIc, respectively, are substantially enantiomerically pure.

Stage 5 is the conversion of products of formulae Ia, Ib or Ic into other products of formulae Ia, Ib or Ic and includes saponification, coupling, and deprotecting reactions. The stereochemistry of the product mixture is the same as that of Stage 4.

Method B is a preferred method relative to Method A.

Stage 1 involves separation of the mixture of racemic diastereomers of formula VI obtained as the product of Method A, Stage 1, by fractional distillation and crystallization to obtain nitroalcohol VI as a substantially pure racemic diastereomer [2(RS),3(SR)] substantially free of the other racemic diastereomer [2(RS),3(RS)]. Reduction of the nitro group by the preferred method of hydrogenation over a 10% palladium on carbon catalyst provides V as one racemic diastereomer [2(RS),3(SR)] substantially free of the other racemic diastereomer. (It will be appreciated by one skilled in the art that, alternatively, the diastereomer [2(RS),3(RS)] may also be used for the production of compounds of this invention.)

Stage 2 is the same as in Method A but uses the amine V prepared as described in Method B, Stage 1. The products obtained by this method are substantially pure [2(RS),3(SR)] mixtures.

Stage 3 is the same as in Method A but uses the product prepared according to Method B, Stage 2. The products obtained by this method are substantially pure [2(RS),3(SR)] mixtures.

As in Method A, the order of steps in Stage 2 and Stage 3 may be altered under appropriate conditions.

Stage 4 is the same as Stage 4 of Method A. The product mixture obtained is the same as the product mixture obtained in Method A, Stage 4.

Stage 5 is the same as that of Method A, Stage 5.

Method C is a method for direct synthesis of individual ("resolved") isomers of formulae Ia, Ib, and Ic which are substantially free of the other diastereomers, for example, for products corresponding to IIa, IIb, and IIc in which the centers corresponding to * and Δ are all S.

Stage 1 involves resolution of the racemate V prepared according to Method B, Stage 1. After the free base corresponding to V is liberated, resolution is carried out by formation of the diastereomeric salts with D-tartaric acid and separation of those salts by fractional crystallization. The desired amine is then obtained from the separated salts by freeing the base to afford, for example, the free base corresponding to 2(R)3(S) in a compound of formula V. The product thus obtained is substantially enantiomerically and diastereomerically pure.

Stages 2 and 3 are substantially the same as Stages 2 and 3 in Methods A and B, but limited to methods which will avoid racemization of centers which correspond to those marked * in formulae IIa, IIb, and IIc. The products thus obtained are essentially enantiomerically and diastereomerically pure.

Stage 4 is limited to methods which will avoid racemization at the centers labelled * and Δ in formulae IIa, IIb and IIc. The preferred method is the use of Dess-Martin periodinane. The products Ia, Ib and Ic thus obtained are essentially enantiomerically and diastereomerically pure.

Stage 5 is limited to methods which will avoid racemization at the centers labelled * and Δ in formulae IIa, IIb and IIc.

Method D

Stage 1 is a separation of compounds of formulae Ia, Ib or Ic prepared by Methods A or B which are diastereomeric mixtures (owing to the 3(RS) center) into their single isomers which are substantially diastereomerically and enantiomerically pure. The preferred method for completing this separation is the use of preparative chromatography, e.g. MPLC and HPLC.

Stage 2 is the same as Stage 5, Method C.

Inhibition Measurements:

The potency of compounds of the invention to act as elastase inhibitors was initially determined by the ability of a compound of the invention to inhibit the action of human leukocyte elastase (HLE) on a low

molecular weight peptide substrate. The potency of an inhibitor is evaluated by obtaining a kinetic determination of the dissociation constant, K_i , of the complex formed from the interaction of the inhibitor with HLE. The substrate used was the anilide methoxysuccinyl-alanyl-alanyl-prolyl-valine-p-nitroanilide as described by K. Nakajima et al. in the J. Biol. Chem., 254: 4027-4032 (1979) and by T. Teshima et al. in J. Biol. Chem., 257: No. 9, 5085-5091 (1982). The HLE enzyme used in these studies may be obtained from

5 Elastin Products of St. Louis, Missouri or can be purified according to B. R. Viscarello et al. in Preparative Biochemistry, Vol. 13, pages 57-67, (1983) as follows, all work having been done in a cold room at 4° C.

Salt Extraction-DNase Treatment: The starting material, 193 g of purulent sputum, was homogenized with 200 ml of cold distilled water and centrifuged at 30,000 x gravity for 20 min. at 4° C. The supernatant

10 was discarded and the pellet extracted with high salt and treated with DNase as per the method of D. Y. Twumasi et al. in J. Biol. Chem., 252: 1917-1926 (1977). Chromatography on Elastin Agarose: The precipitate from the DNase digest was taken up in two 40 ml portions of 50 mM Tris, 1.0 M NaCl, pH 8; the suspension was centrifuged and the resulting supernatant applied directly to a column of soluble elastin-Sephacrose 4B (2.5 x 20 cm). The column was washed with equilibrating buffer (50 mM Tris, 50 mM NaCl,

15 pH 8.0) until the optical density at 280 nm (OD_{280}) of the eluate returned to baseline. Additional contaminating protein was eluted with two column volumes of 50 mM acetate, 1.0 M NaCl, pH 5.0. Elastase and cathepsin G (HLC-G) were finally eluted with 50 mM acetate, 1.0 M NaCl, 20% DMSO, pH 5.0. The column was developed at 6 ml/min with the collection of 10 ml fractions. The active fractions were pooled, dialyzed vs. two 6 liter changes of 50 mM acetate, 0.1 M NaCl, pH 5.5, and concentrated to 40 ml on an Amicon®

20 ultrafiltration unit (YM-10 membrane). CM-Chromatography: The concentrated active fraction was applied to a column of CM-Sephadex® C-50 (2.2 x 10 cm) previously equilibrated with 50 mM acetate, 0.1 M NaCl, pH 5.5 and the column was then washed with this buffer to remove contaminating protein. Elution was continued with 50 mM acetate, 0.2 M NaCl, pH 5.5 and resulted in the displacement of a peak of activity assayed against Bz-Phe-Val-Arg-pNA. HLE was next eluted with the acetate buffer containing 0.45 M NaCl,

25 while elution of HLC-G required the presence of 1.0 M NaCl in the buffer as described by R. Martodam et al. in Preparative Biochemistry, Vol. 9, pages 15-31 (1979). This column was developed at 30 ml/hr with the collection of 5.5 ml fractions. From the thus purified HLE, a standard rate of production of p-nitroaniline was measured at 25° C spectrophotometrically in the visible spectrum at 410 nanometers with automatic data acquisition from a Cary 210 spectrophotometer obtained from Varian Associates. Reactions were initiated by

30 injection of 10 microliters of the HLE solution into a 3 milliliter cuvette containing 2.89 milliliters of buffer (10 millimolar sodium phosphate, 500 millimolar NaCl, pH 7.6), 50 microliters substrate solution in DMSO, and 50 microliters of DMSO. Initial, steady-state reaction velocities of p-nitroaniline production were calculated by a fit of the experimental data to a linear dependence on time by linear least squares. This velocity, determined with no inhibitor present, was used as a standard in the calculation of inhibitor K_i values.

35 Without exception, all of the peptide derivatives of the present invention were found to be "slow-binding" inhibitors of HLE and therefore required special methods of analysis to accurately determine K_i values for their inhibition of HLE (see Williams, J. W. and Morrison, J. F., Meth. Enz. 63, 437 (1979) for a description of these methods.) In a typical experiment, 2.89 ml of buffer (10 millimolar sodium phosphate, 500 millimolar sodium chloride, pH 7.6), 50 microliters of inhibitor solution in DMSO, and 50 microliters of

40 substrate solution in DMSO were added to a 3 milliliter cuvette. The cuvette was stoppered, inverted several times to mix its contents and maintained at (25° C) in the spectrophotometer. After a period of five minutes to allow the reaction solution to come to thermal equilibrium, 10 microliters of stock enzyme solution were added to the cuvette to initiate the reaction. Duplicate or triplicate runs were done at zero inhibitor concentration and at least three non-zero inhibitor concentrations. K_i values were calculated according to

45 methods outlined in the above reference by Williams and Morrison. The K_i values for selected compounds were less than 10^{-7} M.

Animal Models

50 Animal models of emphysema include intratracheal (i.t.) administration of an elastolytic protease to cause a slowly progressive, destructive lesion of the lung. These lesions are normally evaluated a few weeks to a few months after the initial insult. However, these proteases also induce a lesion that is evident in the first few hours. The early lesion is first hemorrhagic, progresses to an inflammatory lesion by the end of the first 24 hours and resolves in the first week post insult. To take advantage of this early lesion, the

55 following model was used.

Hamsters are first lightly anesthetized with Brevital. Phosphate buffered saline (PBS) pH 7.4, either alone or containing 400 µg of human leukocyte elastase (HLE), is then administered directly into the trachea. Twenty-four hours later the animals are killed and the lungs removed and carefully trimmed of

extraneous tissue. Following determination of wet lung weight, the lungs are lavaged with PBS and total lavagable red and white cells recovered are determined. The values for wet lung weights, total lavagable red cells and total lavagable white cells are elevated in a dose-dependent manner following administration of HLE. Compounds that are effective elastase inhibitors can prevent or diminish the severity of the enzyme-induced lesion resulting in lower wet lung weight and reduced values for total lavagable cells, both red and white, relative to administration of HLE alone. Compounds can be evaluated by administering them either with or at various times prior to administration of HLE to determine their utility in preventing an HLE lesion. Compounds of this invention produced statistically significant reductions in wet lung weight and total lavagable cells relative to HLE alone.

Compounds of the present invention exhibited activity in at least one of the tests described above under Inhibition Measurement or Animal Model. It should be noted that there was not always a direct correlation between the activities of the compounds measured as K_i values in the Inhibition Measurement test and the reduced values for total lavagable cells and wet lung weights relative to the administration of HLE alone obtained in the Animal Model test. It is thought that the Animal Model test is more predictive of the activity of such compounds in the treatment of emphysema.

Pharmacokinetics: Male Syrian hamsters (80 to 120g) are injected intravenously with the test compound. Prior to injection and at varying time periods thereafter, they are lightly anesthetized with ether and blood samples of approximately 0.2 ml each are withdrawn by cardiac puncture. The blood is expressed into 2 ml centrifuge tubes and allowed to clot for one hour. The sample is then centrifuged and the serum removed.

Drug levels are determined by first inactivating endogenous elastase inhibitors by incubation of 50 microliters of serum with an equal volume of buffer containing 5 mg/ml bovine pancreatic trypsin for 5 min. The trypsin inactivated serum (10 microliters) is then added to a 0.52 ml cuvette containing buffer made 20 nM with respect to HLE. After an additional 30 min. incubation, the reaction is started by the addition of substrate (350 microliters) (MeOSuc-Ala-Ala-Pro-Val-pNA, 1.6 mM) and the reaction monitored spectrophotometrically at a wavelength of 410 nM. For comparative purposes, serum persistence of the test compounds are determined in the following manner:

Percent inhibition of serum samples were calculated as follows:

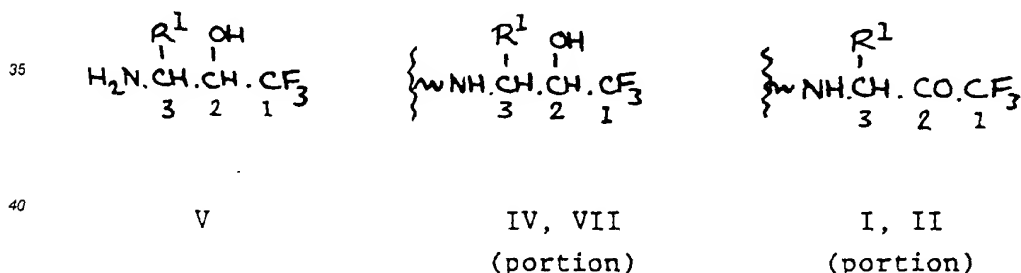
$$\text{percent inhibition} = \frac{V_o - V_i}{V_o} \times 100$$

where V_o is the velocity obtained in the presence of control serum and V_i is the velocity of the inhibited reaction. Data are expressed as log percent inhibition vs. time post inhibitor administration. An approximate serum half-life ($t_{1/2}$) is calculated from the resultant curve.

The compounds of the present invention may be administered to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid arthritis, and osteo arthritis, in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of an osmotic pump, or via a powdered or liquid aerosol. These may be conventionally formulated in an oral or parenteral dosage form by compounding about 10 to 250 mg per unit of dosage with conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted pharmaceutical practice e.g. as described in U.S. Patent No. 3,755,340. For parenteral administration, a 1 to 10 ml intravenous, intramuscular or subcutaneous injection would be given containing about 0.02 to 10 mg/kg of body weight of a compound of the invention 3 or 4 times daily. The injection would contain a compound of the invention in an aqueous isotonic sterile solution or suspension optionally with a preservative such as phenol or a solubilizing agent such as ethylenediaminetetraacetic acid (EDTA). In a powdered aerosol, compounds of the invention may be administered in the same manner as cromolyn sodium via a Spinhaler® turbo-inhaler device obtained from Fisons Corp. of Bedford, Massachusetts at a rate of about 0.1 to 50 mg per capsule, 1 to 8 capsules being administered daily for an average human. Each capsule to be used in the Spinhaler® contains the required amount of a compound of the invention with the remainder of the 20 mg capsule being a pharmaceutically-acceptable carrier such as lactose. In a liquid aerosol, the compounds of the invention are administered at the rate of about 100 to 1000 micrograms per "puff" or activated release of a standard volume of propellant. The liquid aerosol would be given at the rate of 1 to 8 puffs per day with variation in dosages due to the severity of the condition being treated, the weight of the patient and the particle size distribution of the aerosol since smaller particles will achieve greater lung penetration. Propellants, e.g., a fluorinated hydrocarbon or isobutane, containers, valves and actuators for liquid aerosols are described by L. Lachman

et al. in "The Theory and Practice of Industrial Pharmacy", Lea and Febiger, Philadelphia (1976).

In the following Examples and throughout the specification, the following abbreviations and conventions are used: atm (atmospheres); bp (boiling point); °C (degrees Celsius) with all temperatures being in °C unless otherwise noted; g (grams); hr (hours); mg (milligrams); min (minutes); ml (milliliters); l (liters); mol (moles); mmol (millimoles); mp (melting point); bp (boiling point); N (normal); nm (nanometers); nM (nanomolar); satd or sat'd (saturated); aq (aqueous); conc (concentrated); x (times); room temperature (20-23°); DCC (1,3-dicyclohexylcarbodiimide); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); Et₂O (diethyl ether); EtOAc (ethyl acetate); HOAc (acetic acid); HOBT (hydroxybenzotriazole); MeOH (methyl alcohol); EtOH (ethyl alcohol); Pd/C (palladium on charcoal catalyst); pNA (paranitroaniline); THF (tetrahydrofuran); CBZ (benzyloxycarbonyl); t-BOC (tertiarybutyloxycarbonyl); DMF (dimethylformamide); TEA (triethylamine); DCC (1,3-dicyclohexylcarbodiimide); AcOH (acetic acid); S.M. (starting material); NMM (N-methylmorpholine); ≤ (less than or equal to); TEA (triethylamine); TFA (trifluoroacetic acid); Ac₂O (acetic anhydride); CDI (carbonyldiimidazole); WSCDI (water soluble carbodiimide:1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride); DMAP (4-dimethylaminopyridine); Dess-Martin periodinane (1,1,1-triacetoxy-2,1-benzoxiodol-3(3H)-one); HCl gas (gaseous HCl) - otherwise, HCl is an aqueous solution; Rh/C (rhodium on charcoal catalyst); Ø (phenyl group); TLC (thin layer chromatography on silica gel unless otherwise specified); R_f (relative mobility in TLC); MPLC (medium pressure liquid chromatography); HPLC (high pressure liquid chromatography), t_R (HPLC retention time in min), FR (HPLC flow rate in ml/min); Col A (Zorbax® ODS analytical column, 4.6 mm x 25 cm); Col B (Phenomenex® Zorbax® C-8 analytical column, 4.6 mm x 35 cm); Col C (Altex Ultrasphere®/Octyl 10 mm I.D. x 25 cm 5 micron analytical and preparative column); flash chromatography (flash column chromatography on silica gel unless otherwise specified); suction chromatography (suction column chromatography on silica gel). In addition, C, H, N, etc. (the conventional symbols for the elements) are used; 133.3 Pascals = 1 Torr as a conversion factor with 760 Torr = 14.7 pounds per square inch (psi); ¹H NMR (nuclear magnetic resonance) spectra were obtained using either a 80 MHz or 250 MHz instrument and tetramethylsilane (TMS) as an internal standard (the solvent for the particular example is noted in the example), δ (parts per million downfield from TMS); with s (singlet); d (doublet); dd (doublet of doublets); m (multiplet). Nomenclature: For uniformity and clarity, "amino acid sequence type" names are used whenever possible. In addition, amines of formula V and the N-substituents of C-terminal amides of formulae I, II, III, IV, and VII which are formally derived from V are numbered as shown:



When needed or as noted, various examples were repeated if more material was required.

Example 1

2(RS),3(SR)-3-Amino-4-methyl-1,1,1-trifluoro-2-pentanol hydrochloride salt

a. 2-Methyl-1-nitropropane.

1-Iodo-2-methylpropane (94.0 g, 0.51 mol) was added dropwise to a pre-cooled (0°C) suspension of AgNO₃ (100.0 g, 0.65 mol) in Et₂O (180 ml). The reaction was protected from light and stirred overnight as it was allowed to warm to room temperature. The reaction mixture was filtered through Celite®. The filtrate was concentrated under vacuum and the residue was distilled under vacuum (caution: potentially explosive) to give the product (37.7 g, 0.366 mol); b.p. 61-65°C at 6913.6 Pascals (52 mm Hg).

b. 2(RS),3(SR)-4-Methyl-3-nitro-1,1,1-trifluoro-2-pentanol.

1-Nitro-2-methylpropane (37.7 g, 0.366 mol) from Example 1a, trifluoroacetaldehyde ethyl hemiacetal (58.5 g, 0.366 mol, 90% purity) and K_2CO_3 (3.4 g, 0.025 mol) were mixed and stirred at 60 °C for 3 hr. and then at room temperature for 3 days. Brine (75 ml) and 1N aqueous HCl (50 ml) were added and the lower organic layer separated. The aqueous layer was extracted with Et_2O (twice with 250 ml each) and the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with a gradient elution of CH_2Cl_2 :hexane (50:50), CH_2Cl_2 :hexane (75:25), CH_2Cl_2 (100%) and MeOH: CH_2Cl_2 (5:95) to give the product (44.9 g); TLC, R_f = 0.65, silica gel, EtOAc: $CHCl_3$ (5:95).

c. 2(RS),3(SR)-3-Amino-4-methyl-1,1,1-trifluoro-2-pentanol hydrochloride salt.

A solution of a portion of the product of Example 1b (37.0 g, 0.184 mol) in Et_2O (200 ml) was added dropwise to a suspension of lithium aluminum hydride (22.0 g, 0.58 mol) in Et_2O (800 ml). The reaction mixture was stirred for 45 min. and a saturated aqueous solution of Na_2SO_4 (110 ml) was carefully added. The resulting suspension was filtered; the filtrate was treated with ethereal HCl and concentrated under vacuum to give the product (37.6 g) which was used without further purification. 1H NMR data (CD_3COCD_3) (250 MHz): 1.2δ, m, 6H; 2.3δ, m, 1H; 3.58δ, m, 1H; 4.98δ, m, 2H; 7.78δ, m, (NH_2).

Example 2

2(RS),3(SR)-N-[3-(4-Methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide

a. 2(RS),3(SR)-1-[(Phenylmethoxy)carbonyl]-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

A solution of isobutyl chloroformate (11.01 g, 0.08 mol) in dry THF (30 ml) was added dropwise over 5 min to a pre-cooled solution (-15 °C) of CBZ-L-proline (19.21 g, 0.077 mol) and N-methylmorpholine (8.18 g, 0.081 mol) in THF (300 ml) under a nitrogen atmosphere. The reaction mixture was stirred at -15 °C for 15 min. The reaction temperature was then reduced to -40 °C and a solution of a portion of the product of Example 1c (16.00 g, 0.077 mol) and N-methylmorpholine (8.18 g, 0.081 mol) in THF (200 ml) was added dropwise to the reaction. The reaction mixture was stirred at -40 °C for 1 hr. and then allowed gradually to warm to room temperature and stirred for an additional hour. The reaction was filtered and concentrated under vacuum. The resulting syrup was dissolved in $CHCl_3$, and washed with aqueous 20% citric acid (twice with 75 ml each). The organic layer was concentrated under vacuum to give the crude product as a white cloudy syrup. The crude product was triturated with ether: hexane (1:2) to give 3 crops of the product as a white powder (17.11 g); TLC, R_f = 0.47, silica gel, MeOH: $CHCl_3$ (3:97); m.p., 152 ° - 154 ° C; HPLC, t_R = 14.06, 16.63, 18.23, 19.00, Zorbax® ODS analytical column, H_2O : CH_3CN (70:30), flow rate = 3 ml/min.

b. 2(RS),3(SR)-N-[3-(4-Methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

The product of Example 2a (2.00 g, 4.97 mmol) was dissolved in absolute ethanol (50 ml), 10% Pd/C (0.5 g) was added and the reaction mixture was hydrogenolyzed (310126.53 Pascals, 45 psi hydrogen) for 3 hr. at room temperature. The reaction mixture was filtered through Celite® and the solvent was removed under vacuum to give the product (1.36 g) which was used without further purification.

Example 3

2(RS),3(SR)-L-Valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide

a. N-[(Phenylmethoxy)carbonyl]-L-valyl-L-proline methyl ester.

1-Hydroxybenzotriazole (163.3 g, 1.2 mol) was added to a pre-cooled (0 °C) solution of N-benzyloxycarbonyl-L-valine (151.8 g, 0.6 mol) in DMF (1.3 liter) and stirred for 15 min. A suspension of L-proline methyl ester hydrochloride (100.0 g, 0.6 mol) and TEA (64.2 g, 0.63 mol) in DMF (0.7 liter) was added, followed by DCC (137.1 g, 0.66 mol). The reaction mixture was stirred for 3 hr. at 0 °C and then at room temperature for 3 days. The reaction mixture was filtered and the filtrate concentrated under vacuum. The residue was mixed with EtOAc (0.75 liter) and filtered. The filtrate was washed successively with 20%

aqueous citric acid (0.75 liter), saturated aqueous NaHCO_3 , and brine. The organic phase was dried over MgSO_4 , filtered and concentrated under vacuum to give the crude product (271.3 g). The product was purified by flash chromatography on silica gel using a gradient elution starting with CH_2Cl_2 and finishing with $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (4:96) to give the product (218.1 g); TLC, $R_f = 0.48$, silica gel, $\text{MeOH}:\text{CHCl}_3$ (5:95).

5

b. N-[(Phenylmethoxy)carbonyl]-L-valyl-L-proline.

To a solution of a portion of the product of Example 3a (158.8 g, 0.438 mol) in MeOH (1.6 liter) was added 1N aqueous NaOH (500 ml) and the solution stirred at room temperature for 17 hr. 1N aqueous NaOH (100 ml) was added and stirring continued for 5 hr. Additional 1N aqueous NaOH (50 ml) was added and the reaction was stirred overnight. The reaction was concentrated under vacuum to remove the MeOH . H_2O (1.0 liter) was added and the aqueous solution extracted with Et_2O . The aqueous solution was acidified with 1N aqueous HCl (700 ml) and extracted with EtOAc . The EtOAc extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated under vacuum to give the product (159.2 g); TLC, $R_f = 0.34$, silica gel, $\text{MeOH}:\text{CHCl}_3:\text{AcOH}$ (5:94:1).

15

c. 2(RS),3(SR)-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

Isobutylchloroformate (77.3 g, 0.566 mol) was added to a pre-cooled (-15°C) solution of N-methylmorpholine (59.25 g, 0.566 mol) and the product of Example 3b (197.2 g, 0.566 mol) in dry THF (2.5 liters) and the reaction stirred for 10 min. The temperature was reduced to -40°C and N-methylmorpholine (59.25 g, 0.566 mol) was added, followed by the dropwise addition of a solution of the product of Example 1c (117.5 g, 0.566 mol) in THF (2.5 liter). The reaction was allowed to warm to room temperature and stirred for three days. The reaction mixture was filtered and the filtrate concentrated under vacuum. The residue was dissolved in EtOAc and washed successively with H_2O , 1N aqueous HCl and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated to give the crude product (267.8 g). The product was purified by flash chromatography on silica gel using a gradient elution of THF:toluene (5:95) to THF:toluene (25:75) to give the product (183.8 g); TLC, $R_f = 0.4$, silica gel, THF:toluene (20:80).

25

d. 2(RS),3(SR)-L-Valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

A mixture of a portion of the product of Example 3c (36.7 g, 0.073 mol) and 10% Pd/C (10%, 50% water wet) in EtOH (0.6 liter) was hydrogenated on a Parr shaker (303,924 Pascals, 3 atm H_2). After 1 hr. the reaction vessel was evacuated and re-pressurized with H_2 . After an additional 0.5 hr. the reaction mixture was filtered through Celite® and concentrated under vacuum to give the product (26.0 g); TLC, $R_f = 0.16$, silica gel, $\text{MeOH}:\text{CHCl}_3$ (5:95).

30

Example 4

40

2(RS),3(SR)-3-Amino-4-methyl-1,1,1-trifluoro-2-pentanol hydrochloride salt

a. 2-Methyl-1-nitropropane.

An alternative method for making the compound of Example 1a is as follows.

A 5-liter, 3-necked, round-bottomed flask was equipped with a mechanical stirrer, thermometer, addition funnel and N_2 inlet. The flask was charged with AgNO_3 (1006.8, 6.54 mol) in Et_2O (2.5 liter), and isobutyl iodide (927.2 g, 5.03 mol) was placed in the addition funnel. Both the flask and the addition funnel were wrapped in aluminum foil to protect the reaction from light. After the stirred suspension was cooled to approximately 5°C (ice bath), dropwise addition of the iodide over a 2 hr period was begun. The reaction temperature was maintained at or less than 5°C throughout the course of the addition. When the addition was complete, the reaction vessel was packed in ice and allowed to warm slowly to room temperature overnight. NMR analysis of an aliquot taken from the reaction mixture after 48 hr of stirring demonstrated that all of the isobutyl iodide had been consumed. The reaction mixture was filtered through Celite® to remove silver salts and the filter cake was washed with Et_2O (3 x 500 ml). The combined filtrates were dried over MgSO_4 , filtered and concentrated on a rotary evaporator (bath temp = 35°C) to about 600 ml. Fractional distillation (atmospheric pressure) (caution: potentially explosive) gave the purified nitro compound (350.4 g, 68% yield); b.p. $135^\circ\text{C}-142^\circ\text{C}$.

55

b. 2(RS),3(SR)-4-Methyl-3-nitro-1,1,1-trifluoro-2-pentanol.

A 3-liter, 3-necked, round-bottomed flask equipped with a mechanical stirrer and N₂ inlet was charged with K₂CO₃ (470.0 g, 3.4 mol), the product of Example 4a (350.0 g, 3.4 mol) and finally trifluoroacetaldehyde ethyl hemiacetal (708.0 g, 4.4 mol). The mixture was vigorously stirred at room temperature for 76 hr, at which time ¹H-NMR demonstrated the nearly complete consumption of the nitroalkane. The reaction mixture was diluted with CH₂Cl₂ and filtered. The filtrate was treated with aqueous HCl until pH = 3. The layers were separated and the aqueous layer was washed with CH₂Cl₂ (500 ml). The combined CH₂Cl₂ portions were washed with H₂O (1 liter) and brine (1 liter). Drying (MgSO₄) and concentration gave 854.6 g of crude product as a yellow oil. ¹H-NMR showed the two diastereomeric nitro alcohols (present in the ratio of about 3:1 as quantified by integration of the alcohol protons) which consistently appear in the range δ6.0-6.5 when run in acetone-d₆ contaminated by solvents and small amounts of starting materials.

Distillation at reduced pressure gave the following fractions:

| | Wt. | BP (°C) | |
|----|-----------|----------------------------|-----------------|
| 15 | A 191.7 g | 42°-50°C/atm. | S.M. + solvents |
| | B 34.8 g | 35°/1 torr - 45°/.5 torr | |
| 20 | C 213.6 g | 45°/.5 torr - 95°/1.5 torr | |
| | D 337.8 g | 95°/1.5 torr - 105°/2 torr | |
| | E 114.0 g | trap volatiles | |

To simplify purifications in subsequent synthetic steps, an effort was made at this point to obtain the major diastereomeric pair in a substantially pure state and to advance only this material through the sequence. The major diastereomeric pair crystallizes from the mixture of diastereomers, as well as from cold pentane, to yield colorless needles. Thus, fraction C from the above distillation was allowed to crystallize overnight in a refrigerator. The product was collected, washed with cold pentane and dried for several hours in a vacuum oven (Caution! This material is somewhat volatile and significant quantities can be lost under extended vacuum treatment) to give 52.0 g of substantially pure material. The fractions known (by NMR) to contain significant quantities of the desired isomer were repetitively treated in this fashion (and redistilled to provide new fractions further enriched in the desired diastereomer) to eventually obtain a total of 197.7 g of substantially pure nitro alcohol. This amount represents the type of work done, but it does not reflect the upper limit of the yield.

c. 2(RS),3(SR)-3-Amino-4-methyl-1,1,1-trifluoro-2-pentanol hydrochloride salt.

Anhydrous EtOH (232 ml) was added to 10% Pd/C catalyst (2.30 g) under N₂. The product of Example 4b (22.93 g, 0.144 mol) was added and the resultant mixture was placed on a Parr hydrogenation apparatus (about 480,000 Pascals, 55 psi H₂) overnight. Catalyst was removed by filtration through Celite®. The filter cake was then washed with EtOH. HCl gas was bubbled through the combined filtrates until approximately 8 g (about 0.22 mol) were absorbed. The solution was concentrated on a rotary evaporator and the resultant residue was concentrated several times from Et₂O to obtain a white solid. The solid was washed with Et₂O and dried overnight in a vacuum oven to yield 20.79 g (88%) of amine hydrochloride. For the m.p., with slow heating the material softens at 90°C and melts at 118°-120°C. When a sample is plunged into a bath preheated to 110°C, it melts instantaneously.

Example 5

2(RS,3(SR))-L-valyl-L-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide

a. N-[(Phenylmethoxy)carbonyl]-L-valyl-L-proline methyl ester.

*Less active catalysts (e.g., 10% Pd/BaSO₄, wet 10% Pd/C) or insufficient reaction times may lead to the production of one or more by-products.

A solution of CBZ-L-Valine (100.0 g, 0.40 mol) in DMF (1 liter, dried over sieves) was added to a 3-liter, 3-necked, round-bottomed flask equipped with a mechanical stirrer, N₂ inlet and a thermometer. The reaction was cooled to 0 °C and HOBt hydrate (108.1 g, 0.80 mol) was added. Approximately 15 min of stirring were allowed before adding a DMF (500 ml) slurry of L-proline methylester hydrochloride (66.2 g, 0.40 mol) and TEA (41.8 g, 0.42 mol) in one portion. Additional DMF (500 ml) was used to complete the transfer of the slurry. DCC (90.8 g, 0.44 mol) was added to the reaction and was washed down with DMF (100 ml). The reaction was stirred for 3 hr at 0 °C before allowing it to warm to room temperature and stir for 3 days. The reaction mixture was then filtered and the filtrate concentrated at reduced pressure. The filter cake was washed with EtOAc (3 x 1 liter), and concentration of the resultant filtrate gave material that was combined with the residue from concentration of the DMF solution. The combined product mixture (about 2.5 liters) was diluted with Et₂O (2 liters) and stored in the refrigerator overnight. Precipitate was removed by filtration. When the filtrate was washed with 1 N HCl (1 liter), additional precipitate formed and was removed by filtration. The filtrate was then washed with 1 N HCl (1 liter), H₂O (0.5 liter), saturated NaHCO₃ (2 x 1 liter) and brine (0.5 liter). Drying MgSO₄ and concentration gave 587.2 g of crude product. This material was flash chromatographed on silica gel (3.5 kg) with gradient elution (CH₂Cl₂ to 5% MeOH:CH₂Cl₂ (5:95). Mixed fractions were subjected to repeated chromatography to remove impurities. Combination of the fractions containing the desired product gave 500.7 g (87%) of material contaminated with a small amount of low R_f impurity; TLC, R_f=0.37, silica gel, Et₂O:hexane (3:1); R_f=0.53, silica gel, MeOH:CHCl₃ (5:95).

b. N-[(Phenylmethoxy)carbonyl]-L-valyl-L-proline.

A methanolic (4 liters) solution of the product of Example 5a (500.7 g, 1.38 mol) was added to a 12-liter, 3-necked, round-bottomed flask equipped with a mechanical stirrer and an N₂ inlet. To the stirred solution was added 1 N NaOH (1.4 liters), bringing the pH to approximately 13. After the reaction had stirred for 3 hr, the pH dropped to 11. Additional 1 N NaOH (0.1 liter) was used to bring the pH to 12 and the reaction was stirred overnight at room temperature. MeOH was removed from the reaction mixture by concentration on a rotary evaporator. During the course of the solvent removal, a total of 1 liter of H₂O was added to reduce the concentration of the base. The aqueous solution was washed with Et₂O before acidifying with 1 N HCl (1.5 liters) to a pH of approximately 3.5. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 1 liter). The combined organics were washed with brine (1 liter), dried (MgSO₄) and concentrated to give 493.0 g (100%) of product as a white solid; TLC, R_f=0.51, silica gel, MeOH:CHCl₃ (5:95) with added AcOH.

c. 2(RS),3(SR)-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

The product of Example 5b (105.3 g, 0.302 mol) was dissolved in dry THF (1.5 liters) under N₂ in a 3-liter, 3-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, N₂ inlet and an addition funnel. The solution was cooled to -35 °C and treated with 1 equivalent (34 ml, 0.309 mol) of NMM. Isobutyl chloroformate (39 ml, 0.307 mol) was added dropwise over 20 min while maintaining the temperature ≤ -35 °C. After the addition was complete, the reaction was stirred for 1 hr at -35 °C. A second equivalent of NMM (34 ml) was added. The product of Example 4c (62.8 g, 0.302 mol) in THF (300 ml) was then added at such a rate that the temperature was maintained at ≤ -35 °C. After the addition was complete, the temperature was kept ≤ -35 °C for 1 hr before the mixture was allowed to warm to room temperature with stirring overnight. The reaction mixture was filtered and the filter cake was washed with THF (1 liter). The combined filtrates were concentrated to give 189 g of crude product. This material was flash chromatographed on silica gel (5000 ml) and eluted with THF:toluene (1:9). Once product began to elute, the solvent polarity was altered in gradient fashion: THF:toluene (15:85); THF:toluene (20:80); and, finally MeOH:THF:toluene (2.5:30:70) (MeOH use was minimized to prevent the elution of low R_f impurities). Concentration of the column fractions followed by drying under vacuum overnight gave 12.0 g (8%) of slightly impure product and 131.6 g (87%) of substantially pure material. (NOTE: Solutions of this material when taken to complete dryness yielded a foam that eventually solidified under extended vacuum treatment. Care had been taken to accomplish this operation in a large enough flask to accommodate the expansion of the foam.) TLC, R_f=0.25, silica gel, MeOH:CHCl₃ (5:95); R_f=0.37, silica gel, THF:toluene (20:80). When the material is spotted lightly, the two isomers resolved to give spots at R_f=0.37 and R_f=0.46, silica gel, THF:toluene (20:80).

(NOTE: Maintenance of the internal temperatures quoted in this procedure appears to be crucial for

obtaining substantially pure product.)

d. 2(RS),3(SR)-L-Valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

5 The product of Example 5c (131.6 g, 0.262 mol) was dissolved in EtOH (750 ml) and combined with 10% Pd/C catalyst (50% H₂O, 13.0 g) under N₂ in a large Parr hydrogenation bottle. The reaction mixture was shaken under a 480,000 Pascals, 55 psi atmosphere of H₂ on a Parr apparatus. Repressurizing with H₂ was continued until no further uptake was observed. Examination of the reaction by TLC showed complete consumption of starting material. The reaction mixture was filtered through Celite® and concentrated to a
10 foam. This material was triturated with Et₂O, filtered, and dried to give 81.4 g (84%) of light grey solid; TLC, R_f = 0.41, silica gel, CHCl₃:MeOH (10:1).

Example 6

15 3S(orR)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = ØCH₂, R⁴ = H, A = OCO, n = 1)

a. 2R,3S-3-Amino-1,1,1-trifluoro-4-methyl-2-pentanol D-tartaric acid salt.

20 Amine hydrochloride (20 g) generated as in Example 4e was dissolved in H₂O and neutralized with solid NaHCO₃. The aqueous solution was extracted several times with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated to yield the amine free base (14.04 g) as a white solid. This material was combined with D-tartaric acid (12.31 g) in boiling anhydrous EtOH (100 ml), and the resultant cloudy solution was filtered hot through filter paper. The solution was first cooled slowly to room temperature
25 overnight and then placed in the refrigerator for several hours. Precipitate was collected on a fritted funnel, washed with cold EtOH, and dried overnight in a vacuum oven at 40°. A sample of the dried white solid (4.56 g) melted at 127°-130°. Most of this material (4.05 g) was dissolved in boiling EtOH (20 ml), and the solution was slowly cooled to room temperature. The white gel-like solid which deposited was collected in a sintered glass funnel and washed with several portions of EtOH. Vacuum oven drying at 40°C for several
30 hours gave a white solid, m.p., 132°-134°C.

b. 2S,3S-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = ØCH₂, R⁴ = H, A = OCO, n = 1).

35 Acid prepared according to Example 5b (1.00 g, 2.87 mmol) was dissolved in dry THF (16 ml) under N₂ in a 50-ml, 3-necked, round-bottom flask equipped with a thermometer, N₂ inlet, septum and a magnetic stir bar. NMM (0.34 ml, 3.09 mmol) was added and the resultant stirred solution was cooled to an internal temperature of -35°. Isobutyl chloroformate (0.37 ml, 2.85 mmol) was added over 2 min, never allowing the internal temperature to rise above -35°. The reaction was stirred for 1 hr at -45° to -35°. The D-tartrate
40 salt from Example 6a (0.92 g, 2.86 mmol) in a mixture of THF (5 ml) and DMSO (2 ml) was treated with NMM (0.68 ml) and the cloudy solution was added to the reaction mixture at such a rate that the temperature was kept below -40°. The reaction was stirred at -45° to -15° for 1 hr before it was allowed to warm to room temperature overnight. The mixture was diluted with CHCl₃ and then washed (H₂O, sat'd aq NaHCO₃), dried (Na₂SO₄), and concentrated to give the title product (1.15 g, 80%) as a white solid. The ¹H-
45 NMR spectrum of this material in DMSO-d₆ exhibited a doublet at δ6.43, which is the appropriate chemical shift of the alcohol proton in material with the assigned relative configuration.

c. 3S(orR)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = ØCH₂, R⁴ = H, A = OCO, n = 1).

50 A portion of the alcohol generated in Example 6b (0.25 g, 0.5 mmol) was dissolved in CH₂Cl₂ and treated with Dess-Martin periodinane (0.42 g, 0.99 mmol) in a single portion. TFA (0.08 ml, 1.04 mmol) was added, and the slightly turbid mixture was allowed to stir overnight. A white suspension formed in the reaction mixture. Starting material was substantially absent as demonstrated by TLC. Water containing
55 Na₂S₂O₃ (0.78 g) and NaHCO₃ (0.42 g) was added and stirred with the reaction mixture. When the organic layer eventually was cleared of the white solid suspension, it was separated from the aqueous phase. The organic layer was washed (sat'd aq NaHCO₃), dried (Na₂SO₄), and concentrated to give an oil. This material redissolved and was concentrated from Et₂O/hexane to give a white solid (0.21 g, 84% yield). Recrystal-

lization from hot Et₂O/hexane yielded a substantially pure sample of the title compound as a substantially pure isomer which exhibited a single peak on HPLC with a retention time identical with that of an authentic sample of the title product prepared as described in Example 117; HPLC, *t_R* = 5.65, Col A, H₂O:CH₃CH (55:45), FR = 2.0.

Example 7

1-[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-N-[3(RS)-3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 4-Nitrophenyl 2-[tricyclo(3.3.1.1^{3,7})dec-1-yl]ethyl carbonate.

To a solution of p-nitrophenyl chloroformate (1.17 g, 5.82 mmol) in Et₂O (25 ml) at 0 °C was added pyridine (5 ml) followed by addition of 2-(1-adamantyl)ethanol (1.00 g, 5.54 mmol) in Et₂O (20 ml) dropwise over 1 hr. The resulting mixture was stirred at room temperature for 12 hr. and partitioned between H₂O and Et₂O. The ethereal layer was washed with 5% aqueous HCl, pH 7.0 phosphate buffer, dried over MgSO₄, filtered and the solvents removed under vacuum. The crude product was purified by flash chromatography on silica gel eluting with EtOAc:hexane (5:95) to give the product (1.10 g) as a white powder; TLC, *R_f* = 0.29, silica gel, EtOAc:hexane (5:95).

b. 1-[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-N-[2(RS),3(SR)-3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

A solution of the product of Example 7a (731.0 mg, 2.98 mmol), a product using the procedure of Example 2b (500 mg, 1.80 mmol) and K₂CO₃ (2.57 g, 18.6 mmol) in DMF (50 ml) was stirred at room temperature for 18 hr., filtered and the solvent removed under vacuum. The residue was taken up in EtOAc, washed with 3 portions of 10% aqueous NaOH, dried over solid K₂CO₃:Na₂SO₄ (10:90), filtered and the solvent removed at reduced pressure. The crude product was chromatographed on silica gel eluting with MeOH:CHCl₃ (1:99). The resulting solid was washed with hexane to give the product (340 mg) as a white solid; HPLC, *t_R* = 5.86, 6.38, Zorbax® ODS analytical column, Flow rate = 2 ml/min, CH₃CN:H₂O:TFA (70:30:0.1).

c. 1-[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-N-3(RS)-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

To a solution of oxalyl chloride (1.09 g, 8.60 mmol) in dry CH₂Cl₂ (15 ml) cooled to -43 °C was added DMSO (1.37 g, 17.3 mmol) in dry CH₂Cl₂ (10 ml) dropwise over 15 min. The solution was stirred for 10 min. and the product of Example 7b (340 mg, 0.72 mmol) was added in the same manner over 30 min. After stirring the solution at -43 °C for an additional 1 hr, TEA (4.80 ml, 34.5 mmol) was slowly added and the solution allowed to warm slowly to room temperature and was stirred for 2 hr. The solution was diluted with CH₂Cl₂, washed with 10% aqueous HCl, 5% aqueous NaOCl, dried over solid K₂CO₃:Na₂SO₄ (10:90), filtered and the solvent removed under vacuum. The crude product was purified by 2 successive flash chromatographies on silica gel eluting with MeOH:CHCl₃ (0.1:99.9) and EtOAc:hexane (1:5), respectively, to give the product (130 mg) as a white solid; TLC, *R_f* = 0.50, silica gel, MeOH:CHCl₃ (5:95); HPLC, *t_R* = 5.31, Zorbax® ODS analytical column, flow rate = 2 ml/min, CH₃CN:H₂O:TFA (70:30:0.1).

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₂₄ H ₃₅ N ₂ F ₃ O ₄ ·0.25H ₂ O: | C, 60.43; | H, 7.50; | N, 5.87 |
| Found: | C, 60.50; | H, 7.45; | N, 5.74 |

Example 8

3(RS)-1-(4-Phenylbutylcarbonyl)-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 2(RS),3(SR)-1-(4-Phenylbutylcarbonyl)-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

A solution of 5-phenylvaleric acid (0.330 g, 1.86 mmol) and N-methylmorpholine (0.280 g, 2.79 mmol) in THF (100 ml) was cooled to -15 °C. A solution of isobutyl chloroformate (0.280 g, 2.05 mmol) in THF (5 ml) was added dropwise and the mixture was stirred at -15 °C for 10 min., after which the temperature was lowered to -40 °C and a solution of a product made using the procedure of Example 2b (0.500 g, 1.86 mmol) in THF (25 ml) was added dropwise. The mixture was stirred for 1 hr at -40 °C and overnight at room temperature. The mixture was filtered and the filtrate concentrated under vacuum. The crude product was purified by flash chromatography on silica gel eluting with MeOH:CHCl₃ (3:97) to give the product (0.60 g) as a white solid; TLC, R_f = 0.40-0.51, silica gel, MeOH:CHCl₃ (3:97).

b. 3(RS)-1-(4-Phenylbutylcarbonyl)-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (4.22 g, 54.0 mmol) in dry CH₂Cl₂ (80 ml) was added dropwise over 10 min to a pre-cooled (-60 °C), stirred solution of oxalyl chloride (3.43 g, 27.0 mmol) in CH₂Cl₂ (10 ml) under a nitrogen atmosphere. The temperature never exceeded -55 °C during the addition. The mixture was stirred at -60 °C for 15 min. and a solution of the product of Example 8a (0.580 g, 1.35 mmol) in CH₂Cl₂ (100 ml) was added dropwise over 10 min. at -60 °C. The reaction mixture was stirred at -60 °C for 1 hr. Diisopropylethylamine (6.98 g, 54.0 mmol) was added dropwise over 10 min at -60 °C. The reaction mixture was stirred for 1 hr as it warmed to room temperature. The reaction mixture was washed successively with two portions of 1N aqueous HCl and brine, and concentrated under vacuum to give the crude product (0.85 g) as an orange syrup. The crude product was purified by three successive flash chromatographies on silica gel eluting respectively with, 1) MeOH:CHCl₃ (3:97), 2) MeOH:CHCl₃ (3:97), and 3) Et₂O:hexane (90:10) to give the product (319 mg) as a white foam; TLC, R_f = 0.33-0.40, silica gel, Et₂O:hexane (90:10); HPLC, t_R = 17.93, 18.55, Zorbax® ODS analytical column, H₂O:CH₃CN (55:45), flow rate = 2 ml/min.

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₂₂ H ₂₉ N ₂ O ₃ F ₃ .1.25H ₂ O: | C, 58.85; | H, 7.07; | N, 6.24 |
| Found: | C, 58.91; | H, 6.83; | N, 6.13 |

Example 9

3(RS)-1-[(Phenylmethoxy)carbonyl]-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

A solution of dimethylsulfoxide (0.890 g, 11.4 mmol) and dry methylene chloride (5 ml) was added dropwise to a stirred solution of oxalyl chloride (0.75 g, 5.9 mmol) and dry methylene chloride (5 ml) at -60 °C under nitrogen. The reaction mixture was allowed to warm to -25 °C, then a solution of a product made using the process of Example 2a (0.200 g, 0.497 mmol) and dry methylene chloride (5 ml) was added. The resultant mixture was stirred at -25 °C for 0.5 hr. Triethylamine (1.94 g, 19.2 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was filtered. The filtrate was evaporated. The residue was dissolved in chloroform. The chloroform solution was washed successively with 1N aqueous HCl, then brine and dried over Na₂SO₄. The solution was filtered. The solvent was removed under vacuum to give the crude product (0.147 g). The crude product was purified by flash chromatography on silica gel with an eluent of CHCl₃:MeOH (97:3) to give the product (0.11 g); TLC, R_f = 0.25, CHCl₃:EtOAc (90:10).

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| C ₁₉ H ₂₃ F ₃ N ₂ O ₄ .1.5H ₂ O: | C, 53.39; | H, 6.13; | N, 6.55 |
| Found: | C, 53.55; | H, 5.78; | N, 6.56 |

Example 10

2(RS),3(SR)-L-Valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide

(Formula)

a. N-[(Phenylmethoxy)carbonyl]-L-valyl-L-proline methyl ester.

The procedure of Example 3a was repeated.

b. N-[(Phenylmethoxy)carbonyl]-L-valyl-L-proline.

The procedure of Example 3b was repeated using the material from Example 10a.

5 c. 2-Methyl-1-nitropropane.

The procedure of Example 1a was repeated.

d. 2(RS),3(SR)-4-Methyl-3-nitro-1,1,1-trifluoro-2-pentanol.

The procedure of Example 1b was repeated using the material from Example 10c.

e. 2(RS),3(SR)-3-Amino-4-methyl-1,1,1-trifluoro-2-pentanol hydrochloride salt.

10 The procedure of Example 1c was repeated using the material from Example 10d.

f. 2(RS),3(SR)-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)-L-prolinamide].

The process of Example 3c was repeated using the compounds from Examples 10b and 10e.

g. 2(RS),3(SR)-L-Valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)-L-prolinamide].

15 The process of Example 3d was repeated using the compound from Example 10f.

Example 11

3(RS)-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

20

a.-f. Steps a-f were repeated as explained in Examples 10a-f.

g. 3(RS)-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (12.46 g, 159.50 mmol) in dry CH₂Cl₂ (12 ml) was added dropwise over 10 min. to a pre-cooled (-60 °C) stirred solution of oxalyl chloride (10.12 g, 79.75 mmol) in CH₂Cl₂ (160 ml) under a nitrogen atmosphere. The temperature of the reaction never exceeded -50 °C during the addition. A solution or the alcohol in Example 11f (2.00 g, 3.99 mmol) in CH₂Cl₂ (160 ml) was added dropwise over 10 min. at -60 °C. The reaction mixture was stirred at -60 °C for 1 hour. Diisopropylethylamine (20.62 g, 159.50 mmol) was added dropwise over 10 min. at -60 °C. The reaction mixture was stirred for 1 hr. as it warmed to room temperature. The reaction mixture was washed with 1N aqueous HCl, then brine, and then concentrated under vacuum to give the crude product as an orange syrup (2.76 g). The crude product was purified with three successive flash chromatographies on silica gel eluting respectively with 1) ether:hexane (80:20), 2) MeOH:CHCl₃ (2.5:97.5), 3) MeOH:CHCl₃ (2.5: 97.5) to give the product as a white foam (0.88 g); TLC, R_f = 0.45, silica gel, MeOH:CHCl₃ (3:97); HPLC, t_R = 6.45, 11.10, Zorbax® ODS analytical column, H₂O: CH₃CN (55:45) with 0.1% trifluoroacetic acid, flow rate = 2 ml/min.

35

| | | | |
|---|-----------|----------|---------|
| Analysis calculated for: | | | |
| C ₂₄ H ₃₂ N ₃ O ₅ F ₃ ·0.5 H ₂ O: | C, 56.68; | H, 6.54; | N, 8.26 |
| Found: | C, 56.58; | H, 6.52; | N, 8.21 |

40

Example 12

3(RS)-[2-(2-Oxopyrrolidinyl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxypentyl)]-L-prolinamide

45

a. 4-Nitrophenyl-2-(2-oxopyrrolidinyl)ethyl carbonate.

N-(2-hydroxyethyl)-2-pyrrolidone (3.00 g, 23.2 mmol) was dissolved in diethyl ether (20 ml) under a nitrogen atmosphere and stirred at room temperature. A solution of p-nitrophenyl chloroformate (4.68 g, 23.2 mmol) in diethyl ether (25 ml) was added dropwise to the mixture over 2 hr. The mixture was stirred for an additional 2 hr. at room temperature. The mixture was concentrated under vacuum to give the crude product (7.90 g). The crude product was purified by flash chromatography on silica gel with MeOH:CHCl₃ - (5:95) to give the product as a white powder (4.62 g); TLC, R_f = 0.51, silica gel, MeOH:CHCl₃ (3:97).

55

b. 2(RS),3(SR)-[2-(2-Oxopyrrolidinyl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

Potassium carbonate (2.820 g, 40.80 mmol) was added to a solution of ethyl-2-pyrrolidone-p-nitrophenyl

carbonate (1.20 g, 4.08 mmol) and a product made using the procedure of Example 3d (1.50 g, 4.08 mmol) in DMF (100 ml) at room temperature under a nitrogen atmosphere. The reaction was stirred overnight. The reaction mixture was diluted with EtOAc and the excess K_2CO_3 was filtered. The filtrate was concentrated under vacuum to give a residue which was dissolved in EtOAc and washed successively with aqueous 10% $NaHCO_3$, water, aqueous 5% citric acid, and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated under vacuum to give the crude alcohol. The alcohol was purified using flash chromatography on silica gel with MeOH:CHCl₃ (5:95) to give the product (0.72 g); TLC, R_f = 0.46, silica gel, MeOH: CHCl₃ - (7:93).

c. 3(RS)-[2-(2-Oxopyrrolidinyl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxypentyl)]-L-prolinamide.

A solution of DMSO (4.310 g, 55.20 mmol) in dry CH₂Cl₂ (6 ml) was added dropwise over 10 min. to a pre-cooled (-60 °C), stirred solution of oxalyl chloride (3.500 g, 27.60 mmol) in CH₂Cl₂ (80 ml) under a nitrogen atmosphere. The temperature of the reaction never exceeded -50 °C during the addition. A solution of the alcohol from Example 12b (0.720 g, 1.38 mmol) in CH₂Cl₂ (80 ml) was added dropwise over 10 min. at -60 °C. The reaction mixture was stirred at -60 °C for 1 hr. A solution of diisopropylethyl amine (7.13 g, 55.2 mmol) in CH₂Cl₂ (50 ml) was added dropwise over 10 min. at -60 °C. The reaction mixture was stirred for 1 hr. as it warmed to room temperature. The reaction mixture was washed with 1N aqueous HCl and brine and then concentrated under vacuum to give the crude product as an orange syrup. The crude product was purified by flash chromatography on silica gel with MeOH:CHCl₃ (5:95) to give the product as white foam (0.43 g); TLC, R_f = 0.33, silica gel, MeOH:CHCl₃ (5:95); HPLC, t_R = 3.50, 4.63, Zorbax® ODS analytical column, H₂O:CH₃CN (55:45), flow rate = 1 ml/min.

25

| Analysis calculated for: | | | |
|---|-----------|----------|----------|
| C ₂₃ H ₃₅ N ₄ O ₆ F ₃ ·H ₂ O: | C, 51.29; | H, 6.92; | N, 10.40 |
| Found: | C, 51.20, | H, 6.86; | N, 10.03 |

30

Example 13

3(RS)-[2-Methoxycarbonyl]ethylcarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoromethyl-2-oxopentyl)]-L-proinamide

35

a. N-Benzylloxycarbonyl-L-valyl-L-proline t-butyl ester.

A solution of N-benzylloxycarbonyl-L-valine (56.25 g, 0.244 mol) and HOBt (60.67 g, 0.45 mol) in DMF (565 ml) was cooled to 5 °C. DCC (50.89 g, 0.247 mol) was added in one portion. The mixture was stirred an additional 15 min. at 5 °C and then L-proline t-butyl ester (38.36 g, 0.224 mol) was added. The mixture was stirred an additional 2 hr. at 5 °C then for 48 hr. at room temperature. The mixture was filtered and concentrated under vacuum. The oily residue was dissolved in EtOAc (1 liter) and washed successively with 20% aqueous citric acid, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated under vacuum to afford the product (92.0 g) as a white foam; TLC, R_f = 0.9, silica gel, CHCl₃:EtOAc (85:15).

45

b. L-Valyl-L-proline t-butyl ester.

A mixture of the product of Example 13a (92.0 g, 0.227 mol) and 10% Pd/C (10 g) in EtOH (1 liter) was hydrogenated on a Parr shaker for 6 hr. at _____ Pascals, 60 psi at room temperature. The mixture was filtered through Celite® and concentrated under vacuum to afford the product (62 g) as a viscous yellow oil; TLC, R_f = 0.3, silica gel, MeOH:CHCl₃ (10:90).

50

c. N-[2-(Methoxycarbonyl)ethylcarbonyl]-L-valyl-L-proline-1,1-dimethylethyl ester.

55

1N aqueous NaOH (8.0 ml) was added to a precooled (0 °C) solution of the product of Example 13b (2.1 g, 7.8 mmol) in CH₂Cl₂ (60 ml). The mixture was stirred and 3-carbomethoxypropionyl chloride (0.96 ml, 7.8 mmol) was added. The reaction was stirred vigorously for 15 min. at 0 °C. The solution was

removed from the ice bath, diluted with H₂O (30 ml) and acidified with 1N aqueous HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography on a column of silica gel eluting with Et₂O followed by EtOAc to give the product (2.68 g);
 5 TLC, R_f = 0.28, silica gel, Et₂O.

d. N-[2-(Methoxycarbonyl)ethylcarbonyl]-L-valyl-L-proline.

Trifluoroacetic acid (11.0 ml, 143 mmol) was added to a solution of the product of Example 13c (2.68 g, 6.98 mmol) in CH₂Cl₂ (11 ml). The mixture was stirred for 4 hr. and concentrated under vacuum to give the product (2.13 g) which was used without further purification.

e. 2(RS),3(SR)-[2-(Methoxycarbonyl)ethylcarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

15 Isobutylchloroformate (0.85 ml, 6.5 mmol) was added to a pre-cooled (-15 °C) solution of N-methylmorpholine (0.71 ml, 6.5 mmol) and the product of Example 13d (2.13 g, 6.5 mmol) in THF (50 ml). The reaction was stirred for 10 min. and the temperature reduced to -50 °C. A suspension of N-methylmorpholine (0.71 ml, 6.5 mmol) and a product made using the procedure of Example 1c (1.39 g, 6.5 mmol) in
 20 THF (50 ml) was added in one portion and the reaction stirred overnight as it warmed to room temperature. The reaction was filtered and the filtrate concentrated under vacuum. The residue was taken up in EtOAc and washed successively with 1N aqueous HCl and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum. The resulting residue was purified by flash chromatography on silica gel eluting with MeOH:CHCl₃ (5:95) to give the product (1.92 g); TLC, R_f = 0.24, silica gel,
 25 MeOH:CHCl₃ (5:95).

f. 3(RS)-[2-(Methoxycarbonyl)ethylcarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

30 A solution of DMSO (11.2 ml, 0.158 mol) in CH₂Cl₂ (12 ml) was added slowly to a pre-cooled (-60 °C) solution of oxalyl chloride (6.9 ml, 0.079 mol) in CH₂Cl₂ (160 ml). A solution of the product of Example 13e (1.90 g, 3.95 mmol) in CH₂Cl₂ (160 ml) was added to the reaction mixture and stirred for 1 hr. at -60 °C. Diisopropylethylamine (28.0 ml, 0.158 mol) was added slowly and the reaction was allowed to warm to ambient temperature. The solution was washed with 1N aqueous HCl (2 x 80 ml) and brine. The organic
 35 layer was dried over Na₂SO₄, filtered and concentrated to give the crude product (3.5 g). The product was purified by filtration through silica gel with EtOAc followed by flash chromatography on silica gel using MeOH: CHCl₃ (5:95) to give the product (1.49 g); TLC, R_f = 0.31, silica gel, MeOH:CHCl₃ (5:95); Diagnostic ¹H NMR shifts (CD₃SOCD₃, 250 MHz): 0.9, m, 12H; 3.54, s, 3H; 3.54-3.68, m, 2H; 4.34, m, 1H; 4.40, m, 1H; 4.48, dd, $\frac{1}{2}$ H; 4.58, dd, $\frac{1}{2}$ H; 8.1, d, 1H; 8.58, dd, 1H.

40

Example 14

3(RS)-[(2-Carboxyethyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

45 1N aqueous NaOH (0.92 ml) was added to a solution of the product of Example 13f (0.20 g, 0.42 mmol) in MeOH (10 ml) and the reaction was stirred overnight at ambient temperature. 1N aqueous HCl (1 ml) was added and the reaction mixture was concentrated under vacuum to remove MeOH. The aqueous solution remaining was extracted with EtOAc and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum to give the product (0.18 g); TLC, R_f = 0.2, silica gel, MeOH:
 50 CHCl₃:TFA (5:94:1); HPLC, t_R = 2.9, 5.86, Applied Science Absorbosphere® C8, 4.6 mm x 10 cm, CH₃CN:H₂O: TFA (20:80:0.1), flow rate = 1.6 ml/min.

Example 15

55 3(RS)-[(4-(Ethoxycarbonyl)phenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 2(RS),3(SR)-[(4-Ethoxycarbonyl)phenyl]aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypen-

tyl)]-L-prolinamide.

A solution of ethyl 4-isocyanatobenzoate (0.86 g, 4.5 mmol) in CHCl_3 (2 ml) was added dropwise to a solution of a product made using the procedure of Example 3d (1.65 g, 4.5 mmol) in CHCl_3 (20 ml) and the reaction was stirred overnight at ambient temperature. The reaction was concentrated under vacuum to give the crude product. The product was purified by flash chromatography on silica gel using $\text{MeOH}:\text{CHCl}_3$ (2.5:97.5) and $\text{MeOH}:\text{CHCl}_3$ (5:95) as eluents to give the product (1.76 g); TLC, R_f = 0.34, silica gel, $\text{MeOH}:\text{CHCl}_3$ (5:95).

b. 3(RS)-[(4-Ethoxycarbonylphenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (4.5 ml, 63 mmol) in CH_2Cl_2 (5 ml) was added slowly to a pre-cooled (-60°C) solution of oxalyl chloride (2.75 ml, 31.5 mmol) in CH_2Cl_2 (60 ml). The reaction was stirred for 15 min. at -60°C . A solution of the product of Example 15a (1.76 g, 3.15 mmol) in CH_2Cl_2 (60 ml) was added to the reaction mixture and stirred for 1 hr. at -60°C . Diisopropylethylamine (11 ml, 63 mmol) was added slowly and the reaction was allowed to warm to ambient temperature. The solution was washed with 1N aqueous HCl (2 x 60 ml) and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated under vacuum to give the crude product (2.3 g). The product was purified by flash chromatography on silica gel using a step gradient of CHCl_3 , $\text{MeOH}:\text{CHCl}_3$ (2.5:97.5) and $\text{MeOH}:\text{CHCl}_3$ (5:95) to give the product (0.91 g); TLC, R_f = 0.42, silica gel, $\text{MeOH}:\text{CHCl}_3$ (5:95); HPLC, t_R = 6.77, 11.27, Zorbax® ODS analytical column, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (45:55), flow rate = 2 ml/min.

Example 16

3(RS)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

1N aqueous NaOH (1 ml) was added to a solution of the product of Example 15b (0.48 g, 0.86 mmol) in $\text{MeOH}:\text{H}_2\text{O}$ (8 ml:7 ml). The reaction was stirred for 3 hr., additional 1N aqueous NaOH was added (1 ml) and the reaction was stirred overnight at ambient temperature. 1N aqueous HCl (2.5 ml) was added and the methanol was removed under vacuum. H_2O (10 ml) was added to the residue and extracted with EtOAc (2 x 50 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under vacuum to give the product (0.42 g); TLC, R_f = 0.17, silica gel, $\text{MeOH}:\text{CHCl}_3:\text{AcOH}$ (5:94:1); HPLC, t_R = 2.38, 2.78, Zorbax® ODS analytical column, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (30:70), flow rate = 1 ml/min.

Example 17

3(RS)-[(4-Phenylbutyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 2(RS),3(SR)-[(4-Phenylbutyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

DCC (0.906 g, 4.4 mmol) was added to a solution of 5-phenylvaleric acid (0.728 g, 4.08 mmol), a product made using the procedure of Example 3d (1.5 g, 4.08 mmol) and HOBT (1.19 g, 8.8 mmol) in THF (75 ml) at 0°C . The mixture was stirred and allowed to slowly warm to room temperature overnight. The mixture was concentrated under vacuum and the resulting residue was taken up in CHCl_3 (60 ml) and washed successively with 20% aqueous citric acid (30 ml), H_2O (30 ml), 5% aqueous NaHCO_3 (30 ml) and brine (30 ml). The organic phase was collected, dried over Na_2SO_4 , filtered and concentrated under vacuum to give the crude product (2.0 g). Purification by flash chromatography on silica gel eluting with $\text{MeOH}:\text{CHCl}_3$ (5:95) gave the product (1.0 g) as a white foam; TLC, R_f = (0.5-0.55), silica gel, $\text{MeOH}:\text{CHCl}_3$ (5:95).

b. 3(RS)-[(4-Phenylbutyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (3.4 ml, 48 mmol) in dry CH_2Cl_2 (4 ml) was added dropwise to a stirred solution of oxalyl chloride (2.10 ml, 24 mmol) in dry CH_2Cl_2 (50 ml) cooled to -60°C under a N_2 atmosphere. The solution was stirred at -60°C for 15 min. A solution of the product of Example 17a (1.00 g, 1.89 mmol) in dry CH_2Cl_2 (30 ml) was added slowly, keeping the solution temperature below -50°C . The mixture was

stirred at (-50 °C) for 1 hr. Diisopropylethylamine (8.48 ml, 48 mmol) was added dropwise and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was washed successively with 1N aqueous HCl and brine. The organic phase was collected, dried with Na₂SO₄, filtered and concentrated under vacuum to give the crude ketone. The ketone was purified by 3 successive flash chromatographies with silica gel and eluents of (MeOH:CHCl₃ (5:95), CHCl₃ (100%) - MeOH:CHCl₃ (3:97), and Et₂O (100%) - MeOH:Et₂O (10:90) to give the final product (0.2 g) as a white waxy solid; HPLC, t_R = 6.80, 8.90, Zorbax® ODS column; H₂O:CH₃CN:TFA (40:60:0.1), flow rate = 0.75 ml/min.

10

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₇ N ₃ O ₄ F ₃ H ₃₈ .0.5 H ₂ O: | C, 60.65; | H, 7.35; | N, 7.85 |
| Found: | C, 60.68; | H, 7.30; | N, 7.67 |

15

Example 18

3(RS)-2[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

20

a. 4-Nitrophenyl 2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl carbonate.

A product was obtained using the process of Example 7a.

25

b. 2(RS),3(SR)-[2(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

30

A solution of the product of Example 18a (0.758 g, 2.19 mmol), a product made using the procedure of Example 3d (0.768 g, 2.09 mmol) and K₂CO₃ (2.89 g, 20.9 mmol) in DMF (75 ml) was stirred at room temperature for 18 hr., filtered, and the solvents removed under vacuum. The residue was diluted with ethyl acetate, washed with 3 portions of 10% aqueous NaOH and brine, dried over solid K₂CO₃:Na₂SO₄ (10:90), filtered and the solvents removed at reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with MeOH:CHCl₃ (2:98) to give the product (0.965 g) as a white foam; TLC, R_f = 0.14 and 0.18, silica gel, MeOH:CHCl₃ (2:98).

35

c. 3(RS)-[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

40

To a solution of oxalyl chloride (2.14 g, 16.8 mmol) in dry CH₂Cl₂ (30 ml) cooled to -43 °C was added DMSO (2.66 g, 33.6 mmol) in CH₂Cl₂ (20 ml) dropwise over 1 hr., followed by addition of the product of Example 18b (0.965 g, 1.68 mmol) in the same manner over 30 min. After stirring the solution at -43 °C an additional 1 hr., triethylamine (8.50 g, 84.0 mmol) was added and the solution allowed to warm slowly to room temperature. The solution was diluted with CH₂Cl₂, washed with 5% aqueous HCl, 5% aqueous NaOCl, dried over MgSO₄, filtered and the solvent removed under vacuum. The crude product was purified by flash chromatography on silica gel eluting with CHCl₃ after pretreating silica gel with MeOH:CHCl₃ (1:99) to give the product (410 mg) as a white foam; TLC, R_f = 0.39, silica gel, MeOH:CHCl₃ (2:98); HPLC t_R = 8.12 and 10.75, Zorbax® ODS column, flow rate = 1.5 ml/min., CH₃CN:H₂O:TFA (70:30:0.1).

50

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₉ H ₄₄ N ₃ F ₃ O ₅ .0.75 H ₂ O: | C, 59.52; | H, 7.83; | N, 7.18 |
| Found: | C, 59.48; | H, 7.70; | N, 7.17 |

55 Example 19

3(RS)-[2-(2-Methoxyethoxy)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 2-(2-Methoxyethoxy)ethyl 4-nitrophenyl carbonate.

To a solution of p-nitrophenyl chloroformate (2.00 g, 9.92 mmol) in Et₂O (50 ml) at 0 °C was added pyridine (8 ml), followed by addition of 2-(2-methoxyethoxy)ethanol (1.14 g, 9.45 mmol) in Et₂O (25 ml) dropwise over 1 hr. The resulting mixture was stirred at room temperature for 12 hr. and partitioned between H₂O and Et₂O. The ethereal layer was washed with 5% aqueous HCl, pH 7.0 phosphate buffer, dried over MgSO₄, filtered and the solvents removed under vacuum. The crude product was purified by flash chromatography on silica gel eluting with EtOAc:hexane (30:70) to give the product (1.30 g) as a clear colorless oil; TLC, R_f = 0.11, silica gel, EtOAc:hexane (30:70).

b. 2(RS),3(SR)-[2-(2-Methoxyethoxyethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

A solution of the product from Example 19a (1.11 g, 3.90 mmol), a product made using the procedure of Example 3d (1.37 g, 3.72 mmol), and K₂CO₃ (5.14 g, 37.2 mmol) in DMF (100 ml) was stirred at room temperature for 18 hr., filtered and the solvents removed under vacuum. The residue was taken up in ethyl acetate, washed with 3 portions of 10% aqueous NaOH and brine, dried over solid K₂CO₃:Na₂SO₄ (10:90), filtered and the solvents removed under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc after pretreating the silica gel with TEA:hexane (1:9) to give the product (1.13 g) as a clear colorless glass; TLC, R_f = 0.43 and 0.48, silica gel, MeOH:CHCl₃ (1:9).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₂ H ₃₈ N ₃ O ₇ F ₃ : | C, 51.45; | H, 7.45; | N, 8.18 |
| Found: | C, 51.48, | H, 7.35; | N, 8.01 |

c. 3(RS)-[2-(2-Methoxyethoxy)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

To a solution of oxalyl chloride (3.26 g, 2.57 mmol) in dry CH₂Cl₂ (70 ml) cooled to -43 °C was added DMSO (4.07 g, 51.4 mmol) in CH₂Cl₂ (20 ml) dropwise over 1 hr., followed by the addition of the product of Example 19b (1.10 g, 2.14 mmol) in CH₂Cl₂ (25 ml) in the same manner over 30 min. After stirring the solution at -43 °C for an additional 1 hr., TEA (10.80 g, 107.0 mmol) was added and the solution allowed to warm slowly to room temperature. The solution was diluted with CH₂Cl₂, washed with 5% aqueous HCl, 5% aqueous NaOCl, dried over MgSO₄, filtered and the solvents removed under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with MeOH:CHCl₃ (2:98) to give the product (420 mg) as a clear, light yellow syrup; TLC, R_f = 0.32 and 0.37, silica gel, MeOH:CHCl₃ (5:95); HPLC, t_R = 7.38 and 9.55, Zorbax® ODS analytical column, flow rate = 0.5 ml/min, CH₃CN:H₂O: TFA (50:50:0.1).

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₂ H ₃₅ N ₃ O ₇ F ₃ 0.75 H ₂ O: | C, 50.33; | H, 7.20; | N, 8.00 |
| Found: | C, 50.34; | H, 7.21; | N, 7.58 |

Example 20

3(RS)-[(4-Methoxyphenyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 2(RS),3(SR)-[(4-Methoxyphenyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

To a solution of a product made using the procedure of Example 3d (1.50 g, 4.08 mmol) and TEA (2.06 g, 20.4 mmol) in CHCl₃ (50 ml) cooled to 0 °C, was added 4-methoxybenzoyl chloride (0.766 g, 4.49 mmol) in CHCl₃ (40 ml) dropwise over 1 hr. and the solution stirred at room temperature overnight. The solvents were removed under vacuum and the residue taken up in EtOAc, washed with 5% aqueous HCl, 20%

aqueous NaOH, dried over solid $K_2CO_3:Na_2SO_4$ (10:90), filtered, and the solvents removed under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with MeOH:CHCl₃ (5:95) to give the product (1.84 g) as a white foam; TLC, R_f = 0.33, silica gel, MeOH:CHCl₃ (5:95).

5

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $C_{24}H_{34}O_5N_3F_3 \cdot 0.3 H_2O$ | C, 56.86; | H, 6.88; | N, 8.29 |
| Found: | C, 56.80; | H, 6.88; | N, 8.07 |

10

b. 3(RS)-[(4-Methoxyphenyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

To a solution of oxalyl chloride (3.79 g, 29.9 mmol) in dry CH₂Cl₂ (50 ml) cooled to -43 °C was added DMSO (4.73 g, 59.8 mmol) in CH₂Cl₂ (20 ml) dropwise over 40 min., followed by addition of the product of Example 20a (1.50 g, 2.99 mmol) in CH₂Cl₂ (20 ml) in the same manner over 30 min. After stirring the solution at -43 °C for an addition 1 hr., TEA (15.10 g, 149.5 mmol) was added and the solution allowed to warm slowly to room temperature. The solution was diluted with CH₂Cl₂, washed with 5% aqueous HCl, 5% aqueous NaOCl, dried over MgSO₄, filtered and the solvents removed under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc: hexane (1:1) after pretreating the silica gel with TEA:hexane (10:90) to give the product (489 mg) as a white foam; TLC, R_f = 0.15 and 0.19, silica gel, MeOH:CHCl₃ (2:98); HPLC t_R = 6.62 and 9.72, Zorbax® ODS column, flow rate = 1 ml/min., CH₃CN:H₂O:TFA (50:50:0.1).

25

| Analysis calculated for: | | | |
|--------------------------|-----------|----------|---------|
| $C_{24}H_{32}O_5N_3F_3$ | C, 57.71; | H, 6.46; | N, 8.41 |
| Found: | C, 57.39; | H, 6.67; | N, 8.18 |

30

Example 21

3(RS)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 2(RS),3(SR)-N-[3-(4-Methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

A product using the process of Example 2b was obtained.

b. 2(RS),3(SR)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

DCC (0.84 g, 4.09 mmol) was added to a stirred solution of (N²,N⁶-dibenzoyloxycarbonyl)-L-lysine (1.54 g, 3.72 mmol), the product of Example 21a (1.0 g, 3.72 mmol), 1-hydroxybenzotriazole (1.01 g, 7.44 mmol), and dry THF (70 ml) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 hr. and allowed to warm to room temperature slowly overnight. The reaction mixture was filtered, the solvent removed under vacuum and the residue dissolved in CHCl₃. The CHCl₃ solution was washed with 20% aqueous citric acid, the organic layer was dried over Na₂SO₄ and filtered. The solvent was removed under vacuum to give the crude product (3.14 g). The product was purified by flash chromatography on silica gel eluting with CHCl₃:MeOH, (97:3) to afford 1.50 g of the final product, R_f = 0.33-0.45, CHCl₃:MeOH (95:5), silica gel.

50

c. 3(RS)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (3.59 g, 46 mmol) and dry CH₂Cl₂ (30 ml) was added to a stirred solution of oxalyl chloride (3.04 g, 24 mmol) and dry CH₂Cl₂ (50 ml) at -60 °C under nitrogen. The reaction mixture was stirred at -60 °C for 5 min. and was allowed to warm to -30 °C. A solution of the product of Example 21b (1.32 g, 2.0 mmol) and dry CH₂Cl₂ (30 ml) was added dropwise. The resultant reaction mixture was stirred at -25 °C for 1 hr. TEA (7.8 g, 77.4 mmol) was added and the reaction mixture was allowed to slowly warm

to room temperature. The reaction mixture was washed with 1N aqueous HCl, and brine. The organic layer was dried over Na_2SO_4 , filtered, and the solvent removed under vacuum to give the product (2.6 g). The product was purified by flash chromatography (silica gel, CHCl_3 :MeOH, 97:3, to afford the product (0.99 g); TLC, R_f = 0.4-0.52, CHCl_3 :MeOH (95:5), silica gel.

Example 22

3(RS)-[(Phenylmethoxy)carbonyl]-L-phenylalanyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. 2(RS),3(SR)-[(Phenylmethoxy)carbonyl]-L-phenylalanyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

DCC (1.01 g, 4.92 mmol) was added to a stirred solution of a portion of the product of Example 21a (1.41 g, 4.47 mmol), N-(benzyloxycarbonyl)-L-phenylalanine (1.20 g, 4.47 mmol), 1-hydroxybenzotriazole (1.21 g, 8.94 mmol) and dry THF (75 ml) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 hr. and allowed to warm to room temperature and was stirred overnight. The reaction mixture was filtered and the solvent removed under vacuum to give the crude residue which was dissolved in CHCl_3 . The CHCl_3 solution was washed with 20% aqueous citric acid and brine, and dried over Na_2SO_4 . The CHCl_3 solution was filtered and the solvent removed under vacuum to give the crude product (3.57 g). The product was purified by flash chromatography on silica gel, eluting with CHCl_3 :MeOH (97:3) to give the product (1.45 g) as a white foam; TLC, R_f = 0.39-0.60, CHCl_3 :MeOH (95:5), silica gel, HPLC:Zorbax® ODS analytical column, CH_3CN : H_2O (50:50), flow rate = 2.5 ml/min., t_R = 6.47 and 7.63.

b. 3(RS)-[(Phenylmethoxy)carbonyl]-L-phenylalanyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (2.33 g, 29.9 mmol) and dry CH_2Cl_2 (40 ml) was added dropwise to a stirred solution of oxalyl chloride (1.89 g, 14.9 mmol) and dry CH_2Cl_2 (40 ml) at -60 °C under nitrogen. The reaction was stirred at -60 °C for 0.5 hr. A solution of the product of Example 22a (1.43 g, 2.49 mmol) and dry CH_2Cl_2 (40 ml) was added at -50 °C. The resultant mixture was stirred at -60 °C for 1 hr. Diisopropylethylamine (7.70 g, 59.7 mmol) was added and the reaction mixture was allowed to warm to room temperature. The mixture was washed twice with 1N aqueous HCl, then brine. The organic layer was dried over Na_2SO_4 , filtered and the solvent was removed under vacuum to give the crude product (1.87 g). The product was purified by flash chromatography on silica gel, CHCl_3 :MeOH (98:2) to give the product (0.771 g) as a white foam; TLC, R_f = 0.62-0.69, CHCl_3 :MeOH (95:5), silica gel; HPLC:Zorbax® ODS analytical column, CH_3CN : H_2O (50:50), flow rate = 2.5 ml/min., t_R = 6.11 and 6.21.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| $\text{C}_{28}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_5$ | C, 61.41; | H, 5.84; | N, 7.67 |
| Found: | C, 61.53; | H, 5.82; | N, 7.67 |

Example 23

3(RS)-[2-(Methoxycarbonyl)ethylcarbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

a. N-[2-(Methoxycarbonyl)ethylcarbonyl]-L-norleucine.

A solution of 1N sodium hydroxide (100 ml, 100 mmol) was added dropwise to a vigorously stirred mixture of L-norleucine (6.55 g, 50 mmol) and methylene chloride (250 ml) at 0 °C under nitrogen. 3-Carbomethoxypropionyl chloride (7.52 g, 50 mmol) was added dropwise. The resultant reaction mixture was stirred at 0 °C for 15 min. The cooling bath was removed and water (100 ml) was added. The pH was adjusted to 1 with 3N aqueous HCl. Ethyl acetate (200 ml) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the organic layers were combined, washed with brine and dried over Na_2SO_4 . The solution was filtered. The solvent was removed under vacuum to give the crude product (10.73 g). A portion of the crude product (6.47 g, 26.4 mmol) was purified by flash

chromatography on silica gel, CHCl_3 :MeOH, (97:3) to give the product (5.31 g); TLC, R_f = 0.45, silica gel, CHCl_3 :MeOH:AcOH (95:4.75:0.25).

b. 2(RS),3(SR)-[2-(Methoxycarbonyl)ethylcarbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

Dicyclohexylcarbodiimide (3.46 g, 16.8 mmol) was added to a pre-cooled (0 °C) solution of a product made using the procedure of Example 3d (5.60 g, 15.3 mmol), the product of Example 23a (3.75 g, 15.3 mmol) and 1-hydroxybenzotriazole (4.13 g, 30.6 mmol) in THF (70 ml). The resulting solution was allowed to warm slowly to room temperature and stirred overnight. The reaction was filtered and concentrated under vacuum. The residue was diluted with EtOAc and the resulting solution washed with saturated aqueous NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated under vacuum to give the crude product. The product was purified by flash chromatography on a column of silica gel using as eluent a gradient of Et_2O (100%), Et_2O :EtOAc (90:10), Et_2O :EtOAc (75:25), Et_2O :EtOAc (50:50) to give the product (5.6 g); TLC, R_f = 0.45, silica gel, MeOH: CHCl_3 (1:9).

c. 3(RS)-[2-(Methoxycarbonyl)ethylcarbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (27.0 ml, 0.378 mol) in CH_2Cl_2 (27 ml) was added slowly to a pre-cooled (-65 °C) solution of oxalyl chloride (16.5 ml, 0.189 mol) in CH_2Cl_2 (350 ml). The resulting solution was stirred for 15 min. and a solution of the product of Example 23b (5.60 g, 0.00943 mol) in CH_2Cl_2 (250 ml) was added. The reaction was stirred for 1 hr. at -65 °C and diisopropylethylamine (67.0 ml, 0.378 mol) was added dropwise. The reaction was allowed to warm to room temperature and was then washed with 1N aqueous HCl and brine, dried over Na_2SO_4 , filtered and concentrated under vacuum to give the crude product. The crude product was purified by flash chromatography on a column of silica gel eluting with a stepwise gradient of Et_2O (100%), Et_2O :EtOAc (50:50), EtOAc (100%) to give a partially purified product which was further purified by flash chromatography on silica gel eluting with a stepwise gradient of CHCl_3 (100%), MeOH: CHCl_3 (2.5:97.5) and MeOH: CHCl_3 (5:95) to give the final product (3.24 g); HPLC, t_R = 6.80 and 12.98, Zorbax® ODS analytical column, H_2O : CH_3CN (65:35), flow rate = 2 ml/min.

Example 24

3(RS)-[(2-Carboxyethyl)carbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

1N aqueous NaOH (9.5 ml) was added to a solution of the product of Example 23c (2.60 g, 4.39 mmol) in MeOH (95 ml). The reaction was stirred overnight at room temperature and 1N aqueous HCl (10.5 ml) was added. The reaction was concentrated under vacuum and H_2O (35 ml) was added. The suspension was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under vacuum to give the product (2.1 g). HPLC, t_R = 12.63 and 19.05, Zorbax® ODS analytical column, H_2O : CH_3CN (65:35), flow rate = 0.5 ml/min.

Example 25

3(RS)-[(Phenylmethoxy)carbonyl]-L-alpha-glutamyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide phenylmethyl ester

a. 2(RS),3(SR)-[(Phenylmethoxy)carbonyl]-L-alpha-glutamyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide phenylmethyl ester.

Isobutylchloroformate (0.53 ml, 4.1 mmol) was added to a pre-cooled (-15 °C) solution of N-benzyloxycarbonyl-L-glutamic acid- α -benzyl ester (1.52 g, 4.1 mmol) and N-methylmorpholine (0.45 ml, 4.1 mmol) in THF (30 ml). The reaction mixture was stirred for 10 min. and then cooled to -40 °C. A solution of the product of Example 3d (1.5 g, 4.1 mmol) in THF (30 ml) was added dropwise and the reaction was stirred overnight and allowed to warm slowly to room temperature. The reaction was filtered and concentrated under vacuum. The residue was taken up in EtOAc, washed with 1N aqueous HCl and brine, dried over Na_2SO_4 , filtered and concentrated to give the crude product. The product was purified by flash

chromatography on a column of silica gel using as eluant a gradient of CHCl_3 (100%), $\text{MeOH}:\text{CHCl}_3$ - (2.5:97.5) and $\text{MeOH}:\text{CHCl}_3$ (5:95) to give the product (2.13 g); TLC, $R_f = 0.43$, silica gel, $\text{MeOH}:\text{CHCl}_3$ (5:95).

- b. 3(RS)-[(Phenylmethoxy)carbonyl]-L-alpha-glutamyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamidephenylmethyl ester.

A solution of DMSO (8.40 ml, 0.118 mol) in CH_2Cl_2 (8 ml) was added carefully to a pre-cooled (-65°C) solution of oxalyl chloride (5.2 ml, 0.059 mol) in CH_2Cl_2 (100 ml). The solution was stirred for 15 min. and a solution of the product of Example 25a (2.13 g, 2.96 mmol) in CH_2Cl_2 (100 ml) was added dropwise. The reaction was stirred for 1 hr at -60°C and N,N-diisopropylethylamine (20.9 ml, 0.118 mol) was added dropwise. The reaction was allowed to warm to room temperature, washed with 1N aqueous HCl and brine, dried over Na_2SO_4 , filtered and concentrated to give the crude product. The product was partially purified by flash chromatography on a column of silica gel using as eluant a stepwise gradient of Et_2O (100%), $\text{Et}_2\text{O}:\text{EtOAc}$ (50:50) and EtOAc (100%). The product was finally purified by flash chromatography on a column of silica gel using as eluant a stepwise gradient of CHCl_3 (100%), $\text{MeOH}:\text{CHCl}_3$ (1:99), $\text{MeOH}:\text{CHCl}_3$ (2:98), $\text{MeOH}:\text{CHCl}_3$ (3:97) and $\text{MeOH}:\text{CHCl}_3$ (5:95) to give the product (1.35 g); HPLC, $t_R = 7.2$ and 11.5, Zorbax® ODS analytical column, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (50:50), flow rate = 2 ml/min.

Example 26

- 3(RS)-N²-[2-(Methoxycarbonyl)ethylcarbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

- a. N²-[(2-Methoxycarbonyl)ethylcarbonyl]-N⁶-phenylmethoxycarbonyl lysine.

1N aqueous NaOH (43 ml) was added to a pre-cooled (0°C) solution of N-benzyloxycarbonyl-L-lysine (6.06 g, 0.0216 mol) in CH_2Cl_2 (160 ml). The reaction was vigorously stirred and 3-carbomethoxypropionyl chloride (2.66 ml, 0.0216 mol) was added. The reaction was vigorously stirred for 15 min at 0°C . Water (100 ml), 1N aqueous HCl (25 ml) and EtOAc (500 ml) were added successively and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the product (6.78 g). The product was used without further purification.

- b. 2(RS),3(SR)-N²-[2-(Methoxycarbonyl)ethylcarbonyl]-N⁶-phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxypentyl)]-L-prolinamide.

DCC (2.85 g, 13.9 mmol) was added to a mixture of a product made using the procedure of Example 3d (4.63 g, 12.6 mmol), the product of Example 26a (5.00 g, 12.6 mmol), and HOBT (3.76 g, 27.8 mmol) in THF (65 ml) pre-cooled to 0°C . The mixture was stirred at 0°C for 1 hr., warmed to room temperature and stirred overnight. The solvent was removed under vacuum, the residue diluted with EtOAc and washed successively with saturated NaHCO_3 and brine. The organic phase was dried over solid $\text{K}_2\text{CO}_3:\text{Na}_2\text{SO}_4$ (10:90), filtered, and the solvent removed under vacuum to give the crude product. Purification by flash chromatography on silica gel with an eluent of $\text{MeOH}:\text{CHCl}_3$ (1:99) gave the product (6.22 g) as a white foam; TLC, $R_f = 0.40$, silica gel, $\text{MeOH}:\text{CHCl}_3$ (5:95).

- c. 3(RS)-N²-[2-(Methoxycarbonyl)ethylcarbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (15.9 g, 100 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise to a stirred solution of oxalyl chloride (8.8 ml, 200 mmol) in dry CH_2Cl_2 (150 ml) cooled to -43°C under nitrogen. A solution of the product of Example 26b (6.22 g, 8.37 mmol) in CH_2Cl_2 (60 ml) was added in the same manner. The reaction mixture was stirred at -20°C for 1 hr and TEA (70 ml, 400 mmol) was added dropwise. The mixture was allowed to slowly warm to room temperature, stirred for an additional 1 hr and then diluted with CH_2Cl_2 , washed with 5% aqueous NaOCl, dried over solid $\text{K}_2\text{CO}_3:\text{Na}_2\text{SO}_4$ (10:90) filtered and the solvent removed under vacuum to give the crude product. Purification by flash chromatography on silica gel with an eluent of $\text{MeOH}:\text{CHCl}_3$ (1:99) gave the product (4.5 g) as a light yellow foam; TLC, $R_f = 0.51$, silica gel, $\text{MeOH}:\text{CHCl}_3$ (1:9); HPLC, $t_R = 6.99$ and 12.01, flow rate = 1 ml/min, Zorbax® ODS analytical column, $\text{H}_2\text{O}:\text{CH}_3\text{CN}:\text{TFA}$ (50:50:0.1).

Example 27

3(RS)-N²-[(2-Carboxyethyl)carbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

5 A solution of the product of Example 26c (2.0 g, 2.7 mmol) in MeOH (60 ml) and 1N NaOH (5.4 ml, 5.4 mmol) was stirred at room temperature for 12 hr. and then taken to pH 7 with 1N aqueous HCl (6.0 ml, 6.0 mmol). The MeOH was removed under vacuum; the resulting residue was dissolved in EtOAc, washed with brine, dried over MgSO₄, filtered and the solvent removed under vacuum to give the crude product.
 10 Purification by flash chromatography on silica gel (pH 5.5, Baker®) with chloroform gave the product (1.7 g) as a white foam; HPLC, t_R = 4.06 and 5.56, flow rate = 1 ml/min, Zorbax® ODS analytical column, H₂O:CH₃CN:TFA (50:50:0.1).

| | | | |
|--|-----------|----------|---------|
| Analysis calculated for: | | | |
| C ₃₄ H ₄₈ N ₅ O ₉ F ₃ ·1.75 H ₂ O: | C, 53.78; | H, 6.83; | N, 9.22 |
| Found: | C, 53.46; | H, 6.39; | N, 9.03 |

20 Example 28

3S(orR)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide

25 a. 2(RS),3(SR)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-hydroxy-pentyl)]-L-prolinamide.

DCC (0.93 g, 4.49 mmol) was added to a stirred solution of N²-,N⁶-benzyloxycarbonyl-L-lysine (1.69 g, 4.08 mmol), a product made using the procedure of Example 3d (1.50 g, 4.08 mmol), 1-hydroxybenzotriazole (1.10 g, 8.16 mmol) and dry THF (75 ml) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 hr., then was allowed to warm to room temperature and was stirred overnight. The reaction mixture was filtered. The filtrate was evaporated under vacuum. The residue was dissolved in CHCl₃ and the solution was washed with 1N aqueous HCl and brine and was dried over Na₂SO₄. The Na₂SO₄ was filtered and the filtrate was concentrated under vacuum to give the crude product (3.94 g) which was
 30 purified by flash chromatography on silica gel, CHCl₃:MeOH (95:5), to give 2.48 g of product; TLC, R_f = 0.36-0.56, CHCl₃:MeOH (95:5), silica gel; HPLC, Zorbax® ODS analytical column, flow rate = 1.5 ml/min, CH₃CN:H₂O (50:50); t_R = 18.33, 14.99.

| | | | |
|--|-----------|----------|---------|
| Analysis calculated for: | | | |
| C ₃₃ H ₄₁ F ₃ N ₄ O ₇ : | C, 59.01; | H, 6.24; | N, 8.45 |
| Found: | C, 58.89; | H, 6.33; | N, 7.89 |

45 b. 3S(orR)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide.

A solution of DMSO (2.8 g, 36.13 mmol) and dry CH₂Cl₂ (40 ml) was added to a stirred solution of oxalyl chloride and dry CH₂Cl₂ (40 ml) at -60 °C under nitrogen. Then a solution of the product of Example 28a, (2.30 g, 3.01 mmol) and dry CH₂Cl₂ (40 ml) was added to the reaction mixture at -50 °C. The resultant reaction mixture was stirred at -60 °C for 1 hr. Triethylamine (7.290 g, 72.26 mmol) was added and the reaction was allowed to warm to room temperature. The mixture was washed twice with 1N aqueous HCl, then brine and was dried over Na₂SO₄. The Na₂SO₄ was filtered and the filtrate was concentrated under vacuum to give the crude product (2.67 g). The product was purified by flash chromatography on silica gel
 50 with an eluent of CHCl₃:MeOH (97:3) to afford 64 mg of product; TLC, R_f = 0.6, CHCl₃:MeOH (95:5); HPLC, Zorbax® ODS analytical column, CH₃CN:H₂O (60:40), flow rate = 1.5 ml/min, t_R = 5.29.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₃₅ H ₅₀ F ₃ N ₅ O ₈ ·H ₂ O: | C, 58.53; | H, 6.72; | N, 8.98 |
| Found: | C, 58.95; | H, 6.59; | N, 8.74 |

5

Example 29

10 3(RS)-1-(12-Methoxy-12-oxododecyloxy)carbonyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide
 (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = CH₃OCO(CH₂)₁₁, A = OCO, n = 1)

a. Methyl 12-hydroxydodecanoate.

15 A mixture of 1-hydroxydodecanoic acid (4.0 g, 18.5 mmol), MeOH (450 ml), conc H₂SO₄ (2.5 ml), and 3A molecular sieves (3 ml) was stirred at reflux for 16 hr. The mixture was neutralized with sat'd aq NaHCO₃, concentrated under vacuum, and partitioned between Et₂O and water. The ethereal solution was washed (water, sat'd aq NaHCO₃, brine), dried (Na₂SO₄), filtered, and concentrated under vacuum to give the product (3.94 g) as a white solid; NMR (DMSO-d₆) δ83.65 (3H,s); 1.7-1.0 (22H,m).

20 b. 11-Methoxycarbonylundecyl 4-nitrophenyl carbonate.

Using the method of Example 7a, the product of Example 29a was converted into the title compound and purified by flash chromatography (EtOAc:hexane (1:9)) to obtain the title compound in 59% yield; TLC, R_f = 0.20, EtOAc:hexane (1:9).

25

c. 2(RS),3(SR)-1-(12-Methoxy-12-oxododecyloxy)carbonyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = CH₃OCO(CH₂)₁₁, A = OCO, n = 1).

30 Using the method of Example 7b, the product of Example 29b was allowed to react with material prepared using the method of Example 2b to provide, after purification by flash chromatography (acetone:hexane (3:7)), the title product (45%); HPLC, t_R = 4.43, Col A, CH₃CN:H₂O (35:65), FR = 2.0.

d. 3(RS)-1-(12-Methoxy-12-oxododecyloxy)carbonyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = CH₃OCO(CH₂)₁₁, A = OCO, n = 1).

35

To the product of Example 29c (1.1 mmol) was added DMSO (65 ml) and Ac₂O (50 mmol). The resulting solution was stirred 18 hr at room temperature and diluted with Et₂O. The organic solution was washed (sat'd aq NaHCO₃ (3x), water, and brine), dried (Na₂SO₄), filtered, concentrated under vacuum, and purified by flash chromatography (Et₂O:hexane (1:1)) to afford the title product (100%); HPLC, t_R = 12.73, Col A, CH₃CN:H₂O (60:40), FR = 2.0.

40

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₂ H ₂₈ F ₃ N ₃ O ₅ ·0.4H ₂ O: | C, 55.91; | H, 8.00; | N, 5.21 |
| Found: | C, 56.05; | H, 8.00; | N, 5.19 |

45

Example 30

50

3(RS)-1-(12-Hydroxy-12-oxododecyloxy)carbonyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide
 (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = HOCO(CH₂)₁₁, A = OCO, n = 1)

55 Using the method of Example 14 the product of Example 29d was converted into the title product, purified by flash chromatography (EtOAc:hexane (1:1)) and obtained in 10% yield; HPLC, t_R = 4.55, Col A, CH₃CN:H₂O (60:40), FR = 2.0.

| Analysis calculated for: | | | |
|---------------------------------------|-----------|----------|---------|
| $C_{24}H_{39}F_3N_2O_6 \cdot 0.1H_2O$ | C, 56.48; | H, 7.74; | N, 5.49 |
| Found: | C, 56.48; | H, 7.96; | N, 5.23 |

5

Example 31

10 3(RS)-1-[1-Oxo-5-(phenylmethoxycarbonylamino)pentyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = CH(CH_3)CH_3$, $R^3 = \emptyset CH_2 OCONH(CH_2)_4$, $A = CO$, $n = 1$)

a. 5-(Phenylmethoxycarbonylamino)valeric acid.

15 To a stirred, cooled solution (0°) of 5-amino valeric acid (5.00 g, 42.68 mmol) and 2N NaOH (32.0 ml, 32.0 mmol) was added simultaneously benzyl chloroformate (7.65 g, 6.40 ml, 44.81 mmol) and 2N NaOH (32.0 ml, 32.0 mmol). After stirring at 0° for 0.5 hr, the solution was washed with Et_2O . The Et_2O layer was acidified to pH 2.0 with 6N HCl, resulting in the product's precipitating out of solution. The title compound was filtered, washed (H_2O) and dried (vacuum oven) to give the pure product as a white solid (8.55 g, 80.0%), mp $104-105^\circ$; TLC, $R_f = 0.48$, MeOH:CHCl₃:AcOH (3:97:0.1).

20

b. 2(RS),3(SR)-1-[1-Oxo-5-(phenylmethoxycarbonylamino)pentyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = CH(CH_3)CH_3$, $R^3 = \emptyset CH_2 OCONH(CH_2)_4$, $A = CO$, $n = 1$).

25 To a stirred, cooled solution (0°) of the product of Example 31a (0.47 g, 1.86 mmol), HOBT (0.50 g, 3.72 mmol), and DCC (0.40 g, 1.95 mmol) in CHCl₃ (50 ml) was added product prepared using the method of Example 2b (0.50 g, 1.86 mmol). After the reaction mixture had stirred overnight at room temperature, it was filtered and concentrated to afford a syrup which was partially dissolved in EtOAc. The insoluble material was filtered from the EtOAc solution before it was washed (satd aq NaHCO₃, 5% aq citric acid, and brine), dried (Na₂SO₄), and concentrated to a mixture which was purified by flash chromatography (MeOH:CHCl₃ (4:96)) to give the title product as a white foam (0.78 g, 84%); TLC, $R_f = 0.4$, MeOH:CHCl₃ - (4:94).

30

35 c. 3(RS)-1-[1-Oxo-5-(phenylmethoxycarbonylamino)pentyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = CH(CH_3)CH_3$, $R^3 = \emptyset CH_2 OCONH(CH_2)_4$, $A = CO$, $n = 1$).

To the product of Example 31b (1 mmol) was added DMSO (85 mmol) and Ac₂O (64 mmol). The resulting solution was stirred for 18 hr at room temperature, poured into ice water (50 ml) and stirred for 1 to 4 hr. The crude product was extracted into EtOAc; and the EtOAc solution was washed (satd aq NaHCO₃, brine), dried (Na₂SO₄), filtered, and concentrated under vacuum before the product was purified by flash chromatography (CHCl₃:MeOH (97:3)) to afford the product (58%); HPLC, $t_R = 6.56$ & 7.79, Col A, H₂O:CH₃CN (60:40), FR = 2.0.

40

| Analysis calculated for: | | | |
|---------------------------------------|-----------|----------|---------|
| $C_{24}H_{32}F_3N_3O_5 \cdot 1.5H_2O$ | C, 54.74; | H, 6.69; | N, 7.98 |
| Found: | C, 54.87; | H, 6.20; | N, 8.02 |

45

50 Example 32

3(RS)-1-(1-Oxo-4-phenoxybutyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = CH(CH_3)CH_3$, $R^3 = \emptyset O(CH_2)_3$, $A = CO$, $n = 1$)

55 a. 2(RS),3(SR)-1-(1-Oxo-4-phenoxybutyl)-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = CH(CH_3)CH_3$, $R^3 = \emptyset O(CH_2)_3$, $A = CO$, $n = 1$).

To a 0.25 M solution of 4-phenoxybutanoic acid in THF was added a molar equivalent amount of CDI in

one portion. After the reaction mixture was stirred for 1 hr at room temperature, an molar equivalent amount of product prepared using the method of Example 2b was added in one portion. After the reaction was stirred overnight, excess satd aq NaHCO₃ was added; and the mixture was extracted with EtOAc. The EtOAc extracts were washed (in HCl, brine), dried (MgSO₄), filtered, and concentrated under vacuum to afford the title product (88%); TLC, R_f = 0.53 & 0.61, MeOH:CH₂Cl₂ (1:9).

b. 3(RS)-1-(1-Oxo-4-phenoxybutyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = O(CH₂)₃, A = CO, n = 1).

By the method of Example 31c, the product of Example 32a was converted into the title compound in 39% yield after crystallization from water; TLC; R_f = 0.68 & 0.64, CH₂Cl₂:MeOH (9:1).

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₂₁ H ₂₇ F ₃ N ₂ O ₄ · 1.25 H ₂ O: | C, 55.93; | H, 6.59; | N, 6.21 |
| Found: | C, 55.88; | H, 6.67; | N, 6.15 |

Example 33

3(RS)-1-[2-(4-Morpholinyl)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = 4-morpholinyl-(CH₂)₂, A = OCO, n = 1)

a. 2-(4-Morpholinyl)ethyl 4-nitrophenyl carbonate hydrochloride.

Using the method of Example 7a but with the omission of the pyridine (and of the acid wash), 2-(4-morpholinyl)ethanol was treated with 4-nitrophenyl chloroformate. The crude product was filtered, washed with Et₂O, and dried under vacuum. The product obtained (91%) was used for the subsequent reaction without further characterization.

b. 2(RS),3(SR)-1-[2-(4-Morpholinyl)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = 4-morpholinyl-(CH₂)₂, A = OCO, n = 1).

Using the method of Example 7b, the product of Example 33a was allowed to react with product prepared using the method of Example 2b to provide, after purification by flash chromatography (MeOH:CHCl₃ (1:99)), the title product (68%); TLC, R_f = 0.34, MeOH: CHCl₃ (5:95), FR = 2.0.

c. 3(RS)-1-[2-(4-Morpholinyl)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = 4 morpholinyl-(CH₂)₂, A = OCO, n = 1).

To the product (1.1 mmol) of Example 33b was added DMSO (65 mmol) and Ac₂O (50 mmol). The resulting solution was stirred 18 hr at room temperature and diluted with CH₂Cl₂. The organic solution was washed (satd aq NaHCO₃ (3x), water, and brine), dried (Na₂SO₄), filtered and concentrated under vacuum before purification by flash chromatography (MeOH: CHCl₃ (2:98)) to provide the title product (37%); HPLC, t_R = 8.44 & 9.88, Col A, CH₃CN:H₂O (60:40), FR = 2.0.

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₁₈ H ₂₈ F ₃ N ₃ O ₅ · 1.0H ₂ O: | C, 48.97; | H, 6.85; | N, 9.51 |
| Found: | C, 48.97; | H, 6.61; | N, 9.73 |

Example 34

3(RS)-1-[1-Oxo-6-[2-(2-pyridyl)ethoxy]carbonylaminoethyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = (2-pyridyl)-(CH₂)₂OCONH-(CH₂)₅, A = CO, n = 1)

a. 4-Nitrophenyl 2-(2-pyridyl)ethyl carbonate.

A solution of 2-pyridinethanol (1.38 g, 11 mmol) in Et₂O (20 ml) was added over 1 hr to a stirred solution of p-nitrophenylchloroformate (2.26 g, 11 mmol) at 0° under nitrogen. The resulting mixture was stirred for 1 hr at 0° before the precipitate which had formed was collected under a blanket of nitrogen and recrystallized from absolute EtOH to give 1.53 g (58%) of the title compound as off-white crystals, mp 125-127°.

b. 2(RS),3(SR)-1-[1-Oxo-6-[2-(2-pyridyl)ethoxy]carbonylaminoethyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = (2-pyridyl)(CH₂)₂OCONH(CH₂)₅, A = CO, n = 1).

A solution of the amine product of Example 50b (0.75 g, 1.8 mmol), the product of Example 34a (0.675 g, 1.8 mmol), TEA (0.52 ml, 3.6 mmol), CH₃CN (25 ml) and water (25 ml) was stirred at room temperature for 2 days before the solvent was removed under vacuum to afford the crude product which was purified by flash chromatography (CH₃OH:CHCl₃ (2.5:97.5) to provide the product (1.13 mmol, 60%) as a pale yellow solid; TLC, R_f = 0.5, CH₃CH:CHCl₃ (5:95).

c. 3(RS)-1-[1-Oxo-6-[2-(2-pyridyl)ethoxy]carbonylaminoethyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = (2-pyridyl)-(CH₂)₂OCONH(CH₂)₅, A = CO, n = 1).

Using the method of Example 31c, the product of Example 34c was converted into the title product to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (3:97)) the title product in 10% yield; HPLC, t_R = 1.84, Col A, H₂O:CH₃CN (60:40), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|-----------|
| C ₂₅ H ₃₅ F ₃ N ₄ O ₅ .0.5H ₂ O: | C, 55.85; | H, 6.75; | N, 10.40. |
| Found: | C, 56.08; | H, 6.82; | N, 10.43 |

Example 35

3(RS)-1-[2-Phenylmethoxy-1-(phenylmethoxymethyl)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = (ØCH₂OCH₂)₂CH, A = OCO, n = 1)

a. 4-Nitrophenyl 2-phenylmethoxy-1-(phenylmethoxymethyl)ethylcarbonate.

TEA (0.74 g, 7.34 mmol) was added dropwise to a stirred solution of p-nitrophenylchloroformate (1.48 g, 7.34 mmol) and Et₂O (30 ml) between 0° and 5°. To the above reaction mixture a solution of 1,3-dibenzylglycerol (2.0 g, 7.34 mmol) and Et₂O (20 ml) was added between 0° and 5°, and the resulting mixture was stirred for 2 hr between 0° and 5° before it was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered and concentrated under vacuum to leave 3.6 g of yellow oil which was purified by flash chromatography (hexane:Et₂O (8:2)) to give 2.19 g (68%) of the title compound as a clear oil; TLC, R_f = 0.33, hexane:ether (7:3).

b. 2(RS),3(SR)-1-[2-Phenylmethoxy-1-(phenylmethoxymethyl)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = (ØCH₂OCH₂)CH, A = OCO, n = 1).

Using the method of Example 7b, product of Example 35a was allowed to react with the product prepared using the method of Example 2b to provide, after purification by flash chromatography (CHCl₃:EtOAc (95:5)), the title product (62%); HPLC, t_R = 5.81 & 6.29, Col A, H₂O:CH₃CN (40:60), FR = 2.0.

c. 3(RS)-1-[2-Phenylmethoxy-1-(phenylmethoxymethyl)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = (ØCH₂OCH₂)₂CH, A = OCO, n = 1).

Using the method of Example 31c, the product of Example 35b was oxidized to afford, after purification by flash chromatography (CHCl₃:EtOAc (98:2)), the title product (13%); HPLC, t_R = 5.62, col A, H₂O:CH₃CN (40:60), FR = 2.0.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| $C_{29}H_{35}F_3N_2O_6 \cdot 0.25H_2O$ | C, 61.20; | H, 6.28; | N, 4.92 |
| Found: | C, 61.28; | H, 6.34; | N, 5.15 |

Example 36

3(RS)-1-[1-Oxo-4-(1-oxo-2-phenoxyethylamino)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset OCH_2CONH(CH_2)_3$, $A = CO$, $n = 1$)

a. Ethyl 4-(1-oxo-2-phenoxyethylamino)butanoate.

To a stirred mixture of ethyl 4-aminobutanoate hydrochloride (3.4 g) and phenoxyacetyl chloride (2.76 ml) in 50 ml of Et₂O and 50 ml of water was added one portion of NaHCO₃ (4.2 g). After 2 hr the layers were separated and the organic phase was washed (1N HCl, brine), dried (MgSO₄), and filtered. Evaporation of the solvent under vacuum gave 3.1 g (53%) of the title compound as an oil.

b. 4-(1-Oxo-2-phenoxyethylamino)butanoic acid.

A mixture of the product of Example 36a (3.1 g) in 1N NaOH (15 ml) was stirred for 6 hr at room temperature. The resulting solution was made acidic with 2N HCl. The solid which precipitated was collected, washed with water and dried under high vacuum. There was obtained 2.5 g (95%) of the title compound as a white solid, mp. 91-94°.

c. 2(RS),3(SR)-1-[1-Oxo-4-(1-oxo-2-phenoxyethylamino)butyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset OCH_2CONH(CH_2)_3$, $A = CO$, $n = 1$).

Using the method of Example 32a, the product of Example 36b was allowed to react with product prepared using the method of Example 2b to provide, after purification by an acid and base wash workup, the title product (92%); TLC, $R_f = 0.43$ & 0.48 , MeOH:CH₂Cl₂ (1:9).

d. 3(RS)-1-[1-Oxo-4-(1-oxo-2-phenoxyethylamino)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset OCH_2CONH(CH_2)_3$, $A = CO$, $n = 1$).

Using the method of Example 61c, the product of Example 36d was oxidized to afford, after purification by flash chromatography (MeOH: CH₂Cl₂ (3:97)), the title product (75%); HPLC, $t_R = 4.62$ & 6.02 , Col A, CH₃CN:H₂O (65:35), $FR = 2.0$.

Analysis calculated for:

| | | | |
|-------------------------|-----------|----------|---------|
| $C_{23}H_{30}F_3N_3O_5$ | C, 56.26; | H, 6.28; | N, 8.56 |
| Found: | C, 56.28; | H, 6.40; | N, 8.30 |

Example 37

3(RS)-1-(4-Methoxy-1,4-dioxobutyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_3OCO(CH_2)_2$, $A = CO$, $n = 1$)

a. 2(RS),3(SR)-1-(4-Methoxy-1,4-dioxobutyl)-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_3OCO(CH_2)_2$, $A = CO$, $n = 1$).

To a stirred mixture of product prepared using the method of Example 2b (1.34 g) in CH₂Cl₂ (50 ml) and 1N NaOH (6 ml) cooled in an ice-water bath was added dropwise 3-carbomethoxypropionyl chloride (0.75 g). After 1 hr the layers were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated to provide 1.1 g (58%) of the title compound as a white powder; TLC, $R_f = 0.57$, MeOH:CH₂Cl₂ -

(1:9).

b. 3(RS)-1-(4-Methoxy-1,4-dioxobutyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{CH}_3\text{OCO}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 37a was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (2:98)), the title product (71%); TLC, $R_f = 0.58$, MeOH: CH₂Cl₂ - (1:9).

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₁₆ H ₂₃ F ₃ N ₂ O ₅ .0.75H ₂ O: | C, 48.79; | H, 6.27; | N, 7.11 |
| Found: | C, 49.04; | H, 6.12; | N, 6.83 |

Example 38

3(RS)-1-[3-(1,1-Dimethylethoxycarbonyl)amino-1-oxopropyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = (\text{CH}_3)_3\text{COCONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$)

a. 2(RS),3(SR)-1-[3-(1,1-Dimethylethoxycarbonyl) amino-1-oxopropyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = (\text{CH}_3)_3\text{COCONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 32a, 3-(BOC-amino)propanoic acid was allowed to react with product prepared using the method of Example 2b to provide the title product (80%); TLC, $R_f = 0.35$, MeOH:CH₂Cl₂ (1:9).

b. 3(RS)-1-[3-(1,1-Dimethylethoxycarbonyl)amino-1-oxopropyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = (\text{CH}_3)_3\text{COCONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 38a was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (2:98)), the named product (61%); TLC, $R_f = 0.46$, MeOH: CH₂Cl₂ - (1:9).

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₁₉ H ₃₀ F ₃ N ₃ O ₅ .0.75H ₂ O: | C, 50.83; | H, 6.62; | N, 9.39 |
| Found: | C, 51.18; | H, 7.00; | N, 9.28 |

Example 39

3(RS)-1-(3-Benzoylamino-1-oxopropyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{C}_6\text{H}_5\text{CONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$)

a. 2(RS),3(SR)-1-(3-Benzoylamino-1-oxopropyl)-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{C}_6\text{H}_5\text{CONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 32a, 3-(benzoylamino)propanoic acid was allowed to react with product prepared using the method of Example 2b to provide the title product (83%); TLC, $R_f = 0.39$ & 0.42, MeOH:CH₂Cl₂ (1:9).

b. 3(RS)-1-(3-Benzoylamino-1-oxopropyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{C}_6\text{H}_5\text{CONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 39a was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (2:98)), the title product (48%); TLC, $R_f = 0.54$, MeOH:CH₂Cl₂ (1:9).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₁ H ₂₆ F ₃ N ₃ O ₄ : | C, 57.14; | H, 5.94; | N, 9.52 |
| Found: | C, 57.12; | H, 6.59; | N, 9.45 |

Example 40

10 3(RS)-1-[3-(1-Oxo-2,2-diphenylethyl)amino]-1-oxobutyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = \emptyset ₂CHCONH(CH₂)₃, A = CO, n = 1)

a. Ethyl 3-(1-oxo-2,3-diphenylethyl)aminobutanoate.

15 To a stirred solution of ethyl 4-aminobutyrate hydrochloride (2.51 g) and diphenylacetyl chloride (3.46 g) in 50 ml of CH₂Cl₂ was added 50 ml of water followed by the addition of one portion of NaHCO₃ (3.4 g). After 2 hr the layers were separated and the organic phase dried (Na₂SO₄), filtered and evaporated. There was obtained 3.5 g (72%) of the title compound as a white solid; TLC, R_f = 0.71, MeOH: CH₂Cl₂ (5:95).

20 b. 3-(1-Oxo-2,3-diphenylethyl)aminobutanoic acid.

A mixture of the product of Example 40a (3.5 g) in 1N NaOH (30 ml) and EtOH (10 ml) was stirred for 10 hr. The solution was then extracted with Et₂O. The aqueous phase was made acidic with 2N HCl; and the precipitated solid was collected, washed with water and dried under high vacuum. There was obtained 2.9 g (93%) of the title compound as a white powder.

25 c. 2(RS),3(SR)-1-[3-(1-Oxo-2,2-diphenylethyl)amino]-1-oxobutyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = \emptyset ₂CHCONH(CH₂)₃, A = CO, n = 1).

30 Using the method of Example 32a, the product of Example 40b was allowed to react with product prepared using the method of Example 2b to provide the title product (81%); TLC, R_f = 0.13, MeOH:CH₂Cl₂ (5:95).

35 d. 3(RS)-1-[3-(1-Oxo-2,2-diphenylethyl)amino]-1-oxobutyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = \emptyset ₂CHCONH(CH₂)₃, A = CO, n = 1).

Using the method of Example 61c, the product of Example 40c was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (2:98)), the title product (27%); TLC, R_f = 0.24, MeOH: CH₂Cl₂ - (5:95).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₉ H ₃₄ F ₃ N ₃ O ₄ .1.0H ₂ O: | C, 61.31; | H, 6.48; | N, 7.39 |
| Found: | C, 61.58; | H, 6.77; | N, 7.43 |

Example 41

50 3(RS)-1-[2-(2-Methoxyethoxy)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = CH₃O(CH₂)₂O(CH₂)₂, A = OCO, n = 1)

a. 2(RS),3(SR)-1-[2-(2-Methoxyethoxy)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = CH₃O(CH₂)₂O(CH₂)₂, A = OCO, n = 1).

55 Using the method of Example 7b, the product of Example 19a was allowed to react with product prepared using the method of Example 2b to provide, after purification by dry column flash chromatography over silica gel using gradient elution with acetone: hexane from (10:90) to (50:50), the title product (75%); TLC, R_f = 0.30 & 0.35, acetone:hexane (40:60).

b. 3(RS)-1-[2-(2-Methoxyethoxy)ethoxycarbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{CH}_3\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, $A = \text{OCO}$, $n = 1$).

Using the method of Example 61c, the product of Example 41a was oxidized to afford, after purification by flash chromatography (acetone: CHCl_3 (1:3)), the title product (42%); HPLC, $t_R = 5.69$, Col A, H_2O : CH_3CN (75:25), $\text{FR} = 2.0$.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{17}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_6$: | C, 49.39; | H, 6.83; | N, 6.78 |
| Found: | C, 49.27; | H, 6.80; | N, 6.48 |

Example 42

3(RS)-1-[1,4-Dioxo-4-(phenylmethylamino)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{NHCO}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$)

a. 4-Oxo-4-(phenylmethylamino)butanoic acid.

A mixture of benzyl amine (10.7 g) and succinic anhydride (10 g) was stirred in THF (1 liter) for 2 days. The solid was filtered and dissolved in 1N NaOH (110 ml). The aqueous phase was washed with Et_2O and then made acidic with conc HCl while cooling in an ice-water bath. The solid was collected, washed with water and dried under high vacuum. There was obtained 10.9 g (53%) of the title compound as a white powder m.p. 137.5-138°.

b. 2(RS),3(SR)-1-[1,4-Dioxo-4-(phenylmethylamino)butyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{NHCO}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$)

Using the method of Example 32a, the product of Example 42a was allowed to react with product prepared using the method of Example 2b to provide the title compound (74%); TLC, $R_f = 0.48$, $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (1:9).

c. 3(RS)-1-[1,4-Dioxo-4-(phenylmethylamino)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{NHCO}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 42b was oxidized to afford, after purification by flash chromatography ($\text{MeOH}:\text{CH}_2\text{Cl}_2$ (2:98)), the title product (40%); TLC, $R_f = 0.56$, $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (1:9).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{22}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_4$: | C, 58.10; | H, 6.20; | N, 9.23 |
| Found: | C, 57.90; | H, 6.36; | N, 9.27 |

Example 43

3(RS)-1-[1-Oxo-3-(phenylmethoxycarbonylamino)propyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{OCONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$)

a. 2(RS),3(SR)-1-[1-Oxo-3-(phenylmethoxycarbonylamino)propyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{OCONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 32a, CBZ- β -alanine was allowed to react with product prepared using the method of Example 2b to provide the title product (82%); TLC, $R_f = 0.59$, $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (1:9).

b. 3(RS)-1-[1-Oxo-3-(phenylmethoxycarbonylamino)propyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{OCONH}(\text{CH}_2)_2$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 43a was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (2:98)), the title product (35%); TLC, $R_f = 0.23$, MeOH: CH₂Cl₂ - (5:95).

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₂ H ₂₈ F ₃ N ₃ O ₅ · 0.4H ₂ O: | C, 55.20; | H, 6.06; | N, 3.77 |
| Found: | C, 55.28; | H, 6.25; | N, 8.55 |

Example 44

3(RS)-1-[1-Oxo-4-(phenylmethoxycarbonylamino)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{OCONH}(\text{CH}_2)_3$, $A = \text{CO}$, $n = 1$)

a. 2(RS),3(SR)-1-[1-Oxo-4-(phenylmethoxycarbonylamino)butyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{OCONH}(\text{CH}_2)_3$, $A = \text{CO}$, $n = 1$).

Using the method of Example 32a, CBZ-4-aminobutanoic acid was allowed to react with product prepared using the method of Example 2b to provide the title product (72%); TLC, $R_f = 0.47$, Et₂O:EtOAc (1:1).

b. 3(RS)-1-[1-Oxo-4-(phenylmethoxycarbonylamino)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{OCH}_2\text{OCONH}(\text{CH}_2)_3$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 44a was oxidized to afford, after purification by preparative TLC (MeOH:CHCl₃ (2.5:97.5)), the title product (32%); TLC, $R_f = 0.65$ & 0.68 , MeOH:CHCl₃ - (1:9).

Example 45

3R(or S)-1-[1-Oxo-4-phenoxy-2-(2-phenoxyethyl)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = [\text{O}(\text{CH}_2)_2]_2\text{CH}$, $A = \text{CO}$, $n = 1$)

a. Diethyl 2,2-di(2-phenoxyethyl)malonate.

To a stirred solution of sodium (2.3 g) in absolute EtOH (50 ml) was added diethyl malonate (15.2 ml) followed by 2-phenoxyethyl chloride (15.7 g). The reaction mixture was then refluxed for 12 hr. The EtOH was evaporated under vacuum and the mixture diluted with water (40 ml). The aqueous phase was extracted with Et₂O. The combined Et₂O extracts were washed (brine), dried (MgSO₄) filtered and evaporated. Bulb to bulb distillation afforded 12.2 g (27%) of the title diester as a clear liquid, bp 155-175° (106 Pascals, 0.8 Torr); TLC, $R_f = 0.34$, CH₂Cl₂.

b. 4-Phenoxy-2-(2-phenoxyethyl)butanoic acid.

A mixture of the product of Example 45a (10.0 g) and potassium hydroxide (17.7 g) in water (22 ml) was refluxed for 4 hr. The reaction mixture was cooled and acidified with conc HCl. The precipitated solid was collected, washed with water and air dried. The solid obtained (8.44 g) was heated at 170° for 2 hr and then cooled. Recrystallization of the solid from cyclohexane gave 4.1 g (93%) of the title compound as fine white needles; mp 85-86°.

| Analysis calculated for: | | |
|--|-----------|---------|
| C ₁₈ H ₂₀ O ₄ : | C, 71.98; | H, 6.71 |
| Found: | C, 71.92; | H, 6.71 |

5

c. 4-Phenoxy-2-(2-phenoxyethyl)butanoyl chloride.

10 A mixture of the product of Example 45b (1.5 g) and thionyl chloride (0.73 ml) was heated on a steam bath for 1 hr. The reaction mixture was then stripped. The acid chloride title product was obtained as a clear oil in quantitative yield and was used directly.

d. 2(RS),3(SR)-1-[1-Oxo-4-phenoxy-2-(2-phenoxyethyl)butyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = [O(CH₂)₂]₂CH, A = CO, n = 1).

15

Using the method of Example 37a, the product of Example 45c was allowed to react with product prepared using the method of Example 2b to provide the title product (95%); TLC, R_f = 0.47 & 0.54, Et₂O.

20 e. 3R(or S)-[1-Oxo-4-phenoxy-2-(2-phenoxyethyl)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = [O(CH₂)₂]₂CH, A = CO, n = 1).

20

Using the method of Example 61c, the product of Example 45d was oxidized to afford the crude product as a mixture of diastereomers which was separated by flash chromatography (Et₂O:hexane (gradient elution, 60:40 to 75:25)). The faster eluting diastereomer was the title compound, obtained in 27.7% yield; HPLC, t_R = 6.94, Col A, CH₃CN:H₂O (65:35), FR = 2.0.

25

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₉ H ₃₅ F ₃ N ₂ O ₅ : | C, 63.49; | H, 6.43; | N, 5.11 |
| Found: | C, 63.39; | H, 6.47; | N, 5.07 |

30

Example 46

35

3S(or R)-[1-Oxo-4-phenoxy-2-(2-phenoxyethyl)butyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = [O(CH₂)₂]₂CH, A = CO, n = 1)

From the separation of the diastereomers of the crude product described in Example 45e, the slower eluting diastereomer was the title compound here, obtained in 28.3% yield; HPLC, t_R = 5.04, Col A, CH₃CH:H₂O (65:35), FR = 2.0.

40

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₉ H ₃₅ F ₃ N ₂ O ₅ : | C, 63.49; | H, 6.43; | N, 5.11 |
| Found: | C, 63.50; | H, 6.45; | N, 5.26 |

45

Example 47

50

3(RS)-1-[6-[(4-Ethoxycarbonylphenyl)aminocarbonylamino]-1-oxo]hexyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = 4-(CH₃CH₂OCO)ØNHCONH(CH₂)₅, A = CO, n = 1)

55

a. 2(RS),3(SR)-1-[6-[(4-Ethoxycarbonylphenyl)aminocarbonylamino]-1-oxo]hexyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, R¹ = CH(CH₃)CH₃, R³ = 4-(CH₃CH₂OCO)ØNHCONH(CH₂)₅, A = CO, n = 1).

Ethyl p-isocyanatobenzoate (0.288 g, 1.5 mmol) was added to a stirred solution of the product of Example 50b (0.6 g, 1.5 mmol), TEA (0.15 g, 1.5 mmol), and DMF (20 ml) under nitrogen at room temperature. The resulting mixture was stirred at room temperature overnight before it was concentrated under vacuum to leave an amber residue which was dissolved in EtOAc. The EtOAc solution was washed (1N HCl), dried (MgSO₄), filtered, and concentrated under vacuum to leave 1.15 g of oily residue. This residue was purified by flash chromatography (CHCl₃:CH₃OH (97:3)) to give 0.62 g (70%) of the title compound as a white solid; TLC, R_f = 0.28 & 0.35, CHCl₃:CH₃OH (95:5).

b. 3(RS)-1-[6-[(4-Ethoxycarbonylphenyl)aminocarbonylamino]-1-oxo]hexyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = 4-(CH₃CH₂OCO)ØNHCONH(CH₂)₅, A = CO, n = 1).

Using the method of Example 61c the product of Example 47a was oxidized to afford, after purification by flash chromatography (CHCl₃:MeOH (97:3)), the title product (43%); HPLC, t_R = 12.39 & 15.79, Col. A, H₂O:CH₃CN (65:35), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₇ H ₃₇ F ₃ N ₄ O ₆ ·1.0H ₂ O: | C, 55.09; | H, 6.68; | N, 9.51 |
| Found: | C, 54.75; | H, 6.63; | N, 9.29 |

Example 48

3(RS)-1-[6-(Phenylmethoxycarbonylamino)-1-oxohexyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = ØCH₂OC(=O)NH(CH₂)₅, A = CO, n = 1)

Using the method of Example 31c, the product of Example 50a was oxidized to afford, after purification by flash chromatography (CHCl₃:MeOH (97:3)), the title product (31%); HPLC, t_R = 4.06, Col. A, CH₃CN:H₂O (1:1), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₅ H ₃₄ F ₃ N ₃ O ₅ ·0.5H ₂ O: | C, 57.46; | H, 6.75; | N, 8.04 |
| Found: | C, 57.87; | H, 6.24; | N, 7.86 |

Example 49

3(RS)-1-[6-[(4-Hydroxycarbonylphenyl)aminocarbonylamino]-1-oxohexyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = 4-(HOCO)ØNHCONH(CH₂)₅, A = CO, n = 1)

Using the method of Example 14, the product of Example 47b was converted into the title product in 38% yield; HPLC, t_R = 6.24 & 8.0, Col. A, H₂O:CH₃CN (75:25), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₅ H ₃₃ F ₃ N ₄ O ₅ ·2.5H ₂ O: | C, 51.1; | H, 6.50; | N, 9.50 |
| Found: | C, 51.34; | H, 5.93; | N, 8.95 |

Example 50

3(RS)-1-[6-(Phenylsulfonylamino)-1-oxohexyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, R¹ = CH(CH₃)CH₃, R³ = ØS(O₂)NH(CH₂)₅, A = CO, n = 1)

a. 2(RS),3(SR)-1-[6-(Phenylmethoxycarbonylamino)-1-oxohexyl]-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpen-

tyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{ØCH}_2\text{OCONH}(\text{CH}_2)_5$, $A = \text{CO}$, $n = 1$).

DCC (6.35 g, 30.8 mmol) was added to a stirred solution of N-CBZ-aminocaproic acid (6.84 g, 25.7 mmol), material prepared by the method of Example 2b (6.89 g, 25.7 mmol), HOBT (6.94 g, 51.4 mmol) and dry THF (250 ml) at 0°C under nitrogen. The resulting reaction mixture was stirred at 0°C for 1 hr, was allowed to warm to room temperature, and was stirred overnight before it was filtered. The filtrate was concentrated under vacuum to a brown residue which was dissolved in CHCl_3 , and the CHCl_3 solution was washed (20% citric acid solution), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (CHCl_3 :MeOH (97:3)) to give 8.0 g (61%) of the title compound as a waxy solid; TLC, $R_f = 0.35$, CHCl_3 :MeOH (95:5).

b. 2(RS),3(SR)-1-(6-Amino-1-oxohexyl)-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{H}_2\text{N}(\text{CH}_2)_5$, $A = \text{CO}$, $n = 1$).

A mixture of the product of Example 50a (2.06 g, 3.99 mmol), EtOH (100 ml), and 10% Pd/C (0.3 g) was placed on a Parr® shaker under _____ Pascals (45 psi) of H_2 for 3 hr. The mixture was filtered through Celite® and the Celite® cake was washed with EtOH. The EtOH washes and the above filtrate were combined and concentrated under vacuum to give 1.36 g (86%) of the title compound as a pale green waxy oil; TLC, $R_f = 0.2$, CHCl_3 :MeOH (85:15).

c. 2(RS),3(SR)-1-(6-Phenylsulfonylamino-1-oxohexyl)-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{ØS}(\text{O}_2)\text{NH}(\text{CH}_2)_5$, $A = \text{CO}$, $n = 1$).

Benzenesulfonyl chloride (0.6 g, 1.5 mmol) was added to a stirred solution of the product of Example 50b (0.26 g, 1.5 mmol), TEA (0.3 g, 3.0 mmol), and dry DMF (20 ml) under nitrogen at room temperature and the resulting mixture was stirred at room temperature overnight. The DMF was removed under vacuum to leave a brownish residue which was dissolved in EtOAc. The EtOAc solution was washed (1N HCl), dried (MgSO_4), and filtered. The filtrate was concentrated under vacuum to a residue which was purified by flash chromatography (CHCl_3 :MeOH (97:3)) to give 0.48 g (60%) of the title compound as a white powder; TLC, $R_f = 0.30$ & 0.40, CHCl_3 :MeOH (95:5).

d. 3(RS)-1-(6-Phenylsulfonylamino-1-oxohexyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ia, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = \text{ØS}(\text{O}_2)\text{NH}(\text{CH}_2)_5$, $A = \text{CO}$, $n = 1$).

Using the method of Example 8b, the product of Example 50c was oxidized to afford, after purification by flash chromatography (Et_2O :hexane (3:1) followed by a second column using CHCl_3 :MeOH (97:3)), the title product (36%); HPLC, $t_R = 8.48$ & 10.33, CH_3CN : H_2O (35:65), $\text{FR} = 2.0$.

Example 51

3(RS)-(1-Naphthylcarbonyl)-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}(\text{CH}_3)_2$, $R^3 = 1\text{-naphthyl}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$)

a. 2(RS),3(SR)-(1-Naphthylcarbonyl)-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}(\text{CH}_3)_2$, $R^3 = 1\text{-naphthyl}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

According to the method of Example 20a, material prepared by the procedure of Example 3d was allowed to react with 1-naphthalenecarbonylchloride to provide the title compound, isolated in 38% yield after purification by preparative TLC (hexane:Et₂O (4:6)); TLC, $R_f = 0.46$ & 0.41, MeOH: CHCl_3 (5:95).

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| $\text{C}_{27}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_4$: | C, 60.32; | H, 6.37; | N, 7.82 |
| Found: | C, 60.89; | H, 6.21; | N, 7.68 |

b. 3(RS)-(1-Naphthylcarbonyl)-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}(\text{CH}_3)_2$, $R^3 = 1\text{-naphthyl}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

A solution of DMSO (29.7 g, 380 mmol) in CH_2Cl_2 (81 ml) was added slowly to a precooled solution (-43°) of oxalyl chloride (24.0 g, 190 mmol) in CH_2Cl_2 (350 ml), and the resulting solution was stirred for 15 min before a solution of the product of Example 51b (9.4 mmol) in CH_2Cl_2 (83 ml) was added. After the reaction had been stirred 1 hr at -30° , diisopropylethylamine (48.9 g, 380 mmol) was added dropwise; and the reaction mixture was allowed to warm to room temperature before it was washed (1N HCl, 5% aq NaOCl, brine), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by preparative TLC (hexane:Et₂O (40:60)) to afford the title product (38%); HPLC, $t_R = 5.21$ & 7.31, Col. A, $\text{CH}_3\text{CN}:\text{H}_2\text{O}:\text{TFA}$ (50:50:0.1), FR = 1.5.

10

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{27}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_4 \cdot 0.75\text{H}_2\text{O}$ | C, 60.32; | H, 6.37; | N, 7.82 |
| Found: | C, 60.69; | H, 6.21; | N, 7.68 |

15

Example 52

3(RS)-[4-(Methylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = 4\text{-}[\text{CH}_3\text{S}(\text{O}_2)\text{NHCO}]$, $\text{R}^4 = \text{H}$, A = NHCO, $n = 1$)

Using the method of Example 89, material prepared according to the procedure of Example 16 was allowed to react with methane sulfonamide to provide, after purification by flash chromatography over Baker pH 5.0 silica gel (gradient, $\text{CHCl}_3:\text{MeOH}$ (97:3) to (90:10)), the title product (59%), HPLC, $t_R = 2.60$ & 3.33, Col C, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (60:40), FR = 6.0.

30

| Analysis calculated for: | | | |
|--|-----------|----------|----------|
| $\text{C}_{25}\text{H}_{34}\text{F}_3\text{N}_5\text{O}_7 \cdot 0.5\text{H}_2\text{O}$ | C, 48.85; | H, 5.74; | N, 11.39 |
| Found: | C, 49.03; | H, 5.74; | N, 10.86 |

Example 53

35

3(RS)-[2-(4-Morpholinyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = 4\text{-morpholinyl-CH}_2\text{CH}_2$, $\text{R}^4 = \text{H}$, A = OCO, $n = 1$)

a. 2(RS),3(SR)-[2-(4-Morpholinyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = 4\text{-morpholinyl-CH}_2\text{CH}_2$, $\text{R}^4 = \text{H}$, A = OCO, $n = 1$).

Using the method of Example 7b, material prepared by the procedure of Example 3d was allowed to react with material prepared by the procedure of Example 33a to provide the named compound, isolated in 55% yield after purification by flash chromatography ($\text{MeOH}:\text{CHCl}_3$ (2.5:97.5)); HPLC, $t_R = 4.62$ & 5.85, Col. A, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1:1), FR = 2.0.

50

| Analysis calculated for: | | | |
|---|-----------|----------|----------|
| $\text{C}_{23}\text{H}_{39}\text{F}_3\text{N}_4\text{O}_6 \cdot \text{H}_2\text{O}$ | C, 50.91; | H, 7.61; | N, 10.32 |
| Found: | C, 50.95; | H, 7.20; | N, 10.02 |

b. 3(RS)-[2-(4-Morpholinyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = 4\text{-Morpholinyl-CH}_2\text{CH}_2$, $\text{R}^4 = \text{H}$, A = OCO, $n = 1$).

A solution of DMSO (29.7 g, 380 mmol) in CH_2Cl_2 (135 ml) was added to a precooled (-43°) solution of oxalyl chloride (24.0 g, 190 mmol) in CH_2Cl_2 (350 ml) and the resulting solution was stirred for 15 min.

before a solution of the product of Example 53a (9.4 mmol) in CH_2Cl_2 (125 ml) was added. The reaction mixture was allowed to warm from -43° to -20° as it was stirred for one hour; then diisopropylethylamine (48.9 g, 380 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature before it was further diluted with CH_2Cl_2 , washed (aq NaOH of pH = 10), dried ($\text{K}_2\text{CO}_3/\text{Na}_2\text{SO}_4$) and concentrated under vacuum. The residue was purified by flash chromatography ($\text{MeOH}:\text{CHCl}_3$ (2:98)) to afford the title product (18%); HPLC, $t_R = 2.00$ & 2.60, Col. A, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (1:1), $\text{FR} = 2.0$.

| Analysis calculated for: | | | |
|--|-----------|----------|----------|
| $\text{C}_{23}\text{H}_{37}\text{F}_3\text{N}_4\text{O}_6 \cdot 1.5\text{H}_2\text{O}$: | C, 50.26; | H, 7.34; | N, 10.19 |
| Found: | C, 50.49; | H, 6.96; | N, 9.96 |

Example 54

3(RS)-[(2,4-Dichlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide
(Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = 2,4\text{-dichloro}$, $\text{R}^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

a. 2(RS),3(SR)-[(2,4-Dichlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = 2,4\text{-dichloro}$, $\text{R}^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

Using the method of Example 20a, material prepared by the procedure of Example 3d was allowed to react with 2,4-dichlorobenzoyl chloride to provide the title compound, isolated in 98% yield; TLC, $R_f = 0.54$, $\text{MeOH}:\text{CHCl}_3$ (5:95).

b. 3(RS)-[(2,4-Dichlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = 2,4\text{-dichloro}$, $\text{R}^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

A solution of DMSO (29.7 g, 380 mmol) in CH_2Cl_2 (27 ml) was added slowly to a precooled (-65°) solution of oxalyl chloride (24.0 g, 190 mmol) in CH_2Cl_2 (350 ml), and the resulting solution was stirred for 15 min before a solution of the product prepared by the method of Example 54a (9.4 mmol) in CH_2Cl_2 (250 ml) was added. After the reaction had been stirred for 1 hr at -65° , diisopropylethylamine (48.9 g, 380 mmol) was added dropwise; and the reaction mixture was allowed to warm to room temperature before it was washed (1N HCl, brine), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography ($\text{MeOH}:\text{CHCl}_3$ (3:97)) to afford the title product (15%); HPLC, $t_R = 17.93$ & 18.55, Col. A, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (55:45), $\text{FR} = 2.0$.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{23}\text{H}_{28}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_4 \cdot \text{H}_2\text{O}$: | C, 49.65; | H, 5.43; | N, 7.55 |
| Found: | C, 49.95; | H, 5.31; | N, 7.35 |

Example 55

3(RS)-Phenoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = \emptyset$, $\text{R}^4 = \text{H}$, $\text{A} = \text{OCO}$, $n = 1$)

a. 2(RS),3(SR)-Phenoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = \emptyset$, $\text{R}^4 = \text{H}$, $\text{A} = \text{OCO}$, $n = 1$).

Using the method of Example 20a, material prepared by the procedure of Example 3d was allowed to react with phenyl chloroformate to provide the title compound, isolated in 61% yield after purification by flash chromatography ($\text{MeOH}:\text{CHCl}_3$ (5:95)); TLC, $R_f = 0.31$ & 0.36, $\text{MeOH}:\text{CHCl}_3$ (3:97).

b. 3(RS)-Phenoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$, $\text{R}^3 = \emptyset$, $\text{R}^4 = \text{H}$, $\text{A} = \text{OCO}$, $n = 1$).

Using the method of Example 54b, the product of Example 55a was oxidized to afford, after purification by flash chromatography (hexane:Et₂O (15:85)), the title product (37%); HPLC, *t_R* = 2.72 & 3.55, Col A, H₂O:CH₃CN (1:1), FR = 2.0.

5

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₃ H ₃₀ F ₃ N ₃ O ₅ ·0.5H ₂ O: | C, 55.86; | H, 6.32; | N, 8.50 |
| Found: | C, 56.07; | H, 6.30; | N, 8.48 |

10

Example 56

3(RS)-[2-(2-Pyridyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide
 (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 2-pyridyl-CH₂CH₂, R⁴ = H, A = OCO, n = 1)

15

a. 2(RS),3(SR)-[2-(2-Pyridyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 2-pyridyl-CH₂CH₂, R⁴ = H, A = O, n = 1).

20

Using the method of Example 34b, material prepared by the procedure of Example 3d was allowed to react with material prepared by the procedure of Example 34a to provide the named compound, isolated in 50% yield after purification by flash chromatography (MeOH:CHCl₃ (4:96)); TLC, R_f = 0.30 & 0.34, CHCl₃:MeOH (95:5).

25

b. 3(RS)-[2-(2-Pyridyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 2-pyridyl-CH₂CH₂, R⁴ = H, A = OCO, n = 1).

30

Using the method of Example 54b, with omission of the acid wash, the product of Example 56a was oxidized to afford, after purification by flash chromatography twice (hexane:Et₂O (1:1), then MeOH: CHCl₃ - (5:95)), the title product (19%); HPLC, *t_R* = 9.52 & 14.58, Col.A, H₂O:CH₃CN (60:40), FR = 1.0.

35

| Analysis calculated for: | | | |
|---|-----------|----------|----------|
| C ₂₄ H ₃₃ F ₃ N ₄ O ₅ ·0.75H ₂ O: | C, 54.59; | H, 6.58; | N, 10.61 |
| Found: | C, 54.63; | H, 6.47; | N, 10.55 |

Example 57

40

3(RS)-[(4-Fluorophenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide
 (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 4-F, R⁴ = H, A = NHCO, n = 1)

45

a. 2(RS),3(SR)-[(4-Fluorophenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 4-F, R⁴ = H, A = NHCO, n = 1).

50

Using the method of Example 15a, material prepared by the procedure of Example 3d was allowed to react with 4-fluorophenylisocyanate to provide the title compound, isolated in 84% yield after purification by flash chromatography (gradient, MeOH:CHCl₃ (2.5:97.5) to (5:95)); TLC, R_f = 0.37, MeOH:CHCl₃ (5:95).

55

b. 3(RS)-[(4-Fluorophenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 4-F, R⁴ = H, A = NHCO, n = 1).

Using the method of Example 54b, the product of Example 57a was oxidized to afford, after purification by flash chromatography (MeOH:CHCl₃ (3:97)) the title product (42%); HPLC, *t_R* = 8.87 & 12.10, Col A, H₂O:CH₃CN (60:40), FR = 1.0.

| Analysis calculated for: | | | |
|--|-----------|----------|----------|
| C ₂₃ H ₃₀ F ₄ N ₄ O ₄ : | C, 54.97; | H, 6.02; | N, 11.15 |
| Found: | C, 55.18; | H, 6.15; | N, 11.08 |

5

Example 58

10 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R₂ = CH(CH₃)₂, R³ = 4-[0S(O₂)NHCO]0, R⁴ = H, A = NHCO, n = 1)

15 Using the method of Example 89, material prepared according to the procedure of Example 16 was allowed to react with benzene sulfonamide to provide, after purification by flash chromatography on Baker pH 5.0 silica gel (CHCl₃:MeOH (97:3)), the title product (42%); HPLC, t_R = 4.05 & 5.93, Col C, H₂O:CH₃CN (60:40), FR = 6.0.

| Analysis calculated for: | | | |
|---|-----------|----------|----------|
| C ₃₀ H ₃₆ F ₃ N ₅ O ₇ * 0.5H ₂ O: | C, 53.25; | H, 5.51; | N, 10.34 |
| Found: | C, 53.38; | H, 5.61; | N, 10.02 |

20

25 Example 59

3(RS)-[2-(3-Thiophenyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 3-thiophenyl-CH₂CH₂, R⁴ = H, A = OCO, n = 1)

30 a. 4-Nitrophenyl 2-(3-thiophenyl)ethyl carbonate.

Using the method of Example 7a, 3-thiopheneethanol was treated with 4-nitrophenyl chloroformate to afford, after purification by flash chromatography (EtOAc:hexane (1:9)), the title product (56%); TLC, R_f = 0.25, EtOAc:hexane (1:9).

35

b. 2(RS),3(SR)-[2-(3-Thiophenyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 3-thiophenyl-CH₂CH₂, R⁴ = H, A = 0, n = 1).

40 Using the method of Example 7b, material prepared by the procedure of Example 3d was allowed to react with the product of Example 59a to provide the title compound, isolated in 58% yield after purification by flash chromatography (acetone: hexane (3:7)); TLC, R_f = 0.23 & 0.27, MeOH:CHCl₃ (5:95).

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₄ H ₃₄ F ₃ N ₃ O ₅ S: | C, 52.96; | H, 6.57; | N, 8.06 |
| Found: | C, 53.28; | H, 6.46; | N, 7.77 |

45

50 c. 3(RS)-[2-(3-Thiophenyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 3-thiophenyl-CH₂CH₂, R⁴ = H, A = OCO, n = 1).

55 A solution of DMSO (29.7 g, 380 mmol) in CH₂Cl₂ (135 ml) was added slowly to a precooled (-43°) solution of oxalyl chloride (24.0 g, 190 mmol) in CH₂Cl₂ (350 ml). The resulting solution was stirred 15 min before a solution of material prepared by the method of Example 59b (9.4 mmol) in CH₂Cl₂ (125 ml) was added and the reaction was stirred at -43° for an additional hour. Diisopropylethylamine (48.9 g, 380 mmol) was added dropwise, and the reaction mixture was allowed to warm to room temperature before it was washed (1N aq HCl, 5% aq NaOCl, brine), dried (Na₂SO₄), filtered, and concentrated under vacuum.

Purification of the residue by flash chromatography (acetone:hexane (1:4)) afforded the title product (23%); HPLC, t_R = 5.09 & 7.61, Col A, $H_2O:CH_3CN$ (1:1), FR = 2.0.

Analysis calculated for:

| | | | |
|----------------------------|-----------|----------|---------|
| $C_{24}H_{32}F_3N_3O_5S$: | C, 53.17; | H, 6.21; | N, 8.09 |
| Found: | C, 52.92; | H, 6.26; | N, 8.09 |

Example 60

3(RS)-(1,1-Dimethylethoxycarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_2CH_3$, $R^3 = CH_3C(CH_3)_2$, $R^4 = H$, A = OCO, n = 1)

a. 2(RS),3(SR)-(1,1-Dimethylethoxycarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIb, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_2CH_3$, $R^3 = CH_3C(CH_3)_2$, $R^4 = H$, A = OCO, n = 1).

DCC (5.90 g, 28.7 mmol) was added to a stirred solution of HOBT (7.76 g, 57.4 mmol), BOC- α -aminobutanoic acid (5.60 g, 27.4 mmol), and material prepared by the procedure of Example 2b (7.00 g, 26.1 mmol) in dry THF (130 ml) at 0° under nitrogen. After the resulting reaction mixture had been stirred at 0° for 1 hr, it was allowed to warm to room temperature and was stirred overnight. The reaction mixture was filtered; and the filtrate was concentrated under vacuum to a residue which was redissolved in EtOAc. The resulting solution was washed satd $NaHCO_3$ brine, dried (Na_2SO_4), filtered, and concentrated under vacuum to a residue which was purified by flash chromatography (EtOAc: CH_2Cl_2 (1:3)) to give the title compound (95%); TLC, R_f = 0.29, EtOAc: CH_2Cl_2 (3:7).

b. 3(RS)-(1,1-Dimethylethoxycarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_2CH_3$, $R^3 = CH_3C(CH_3)_2$, $R^4 = H$, A = OCO, n = 1).

Using the method of Example 61c the product of Example 60a was oxidized to afford, after purification by flash chromatography ($MeOH:CHCl_3$ (1.5:98.5), the title product (47%); HPLC, t_R = 10.21 & 14.54, Col A, $H_2O:CH_3CN$ (65:35), FR = 2.0.

Analysis calculated for:

| | | | |
|---------------------------|-----------|----------|---------|
| $C_{20}H_{32}F_3N_3O_5$: | C, 53.21; | H, 7.14; | N, 9.31 |
| Found: | C, 53.65; | H, 7.21; | N, 9.51 |

Example 61

3(RS)-[1-Oxo-2-(2-thiophenyl)ethyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_2CH_3$, $R^3 = (2-thiophenyl)CH_2$, $R^4 = H$, A = CO, n = 1)

a. 2(RS),3(SR)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide trifluoroacetic acid salt (Formula IVb, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_2CH_3$, $R^4 = H$, n = 1).

A solution of material prepared by the procedure of Example 60a (4.0 g, 8.84 mmol) and TFA (32 ml, 415 mmol) in CH_2Cl_2 (32 ml) was stirred at room temperature for 22 hr before the solvents were removed under reduced pressure to afford the crude product (5 g, >100%) as a colorless glass which was used without further purification or characterization.

b. 2(RS),3(SR)-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIb, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_2CH_3$, $R^3 = (2-thiophenyl)CH_2$, $R^4 = H$, A = CO, n = 1).

DCC (0.315 g, 1.53 mmol) was added to a stirred solution of HOBT (0.413 g, 3.06 mmol) 2-

thiopheneacetic acid (0.222 g, 1.53 mmol), NMM (0.154 g, 1.53 mmol), and material prepared according to Example 61a (0.650 g, 1.39 mmol) in dry THF (20 ml) at 0° under nitrogen. After the resulting reaction mixture had been stirred at 0° for 1 hr, it was allowed to warm to room temperature and was stirred overnight. The reaction mixture was filtered; and the filtrate was concentrated under vacuum to a residue which was dissolved in EtOAc. The resulting solution was washed (brine), dried (Na₂SO₄), filtered, and concentrated under vacuum to a residue which was purified by flash chromatography (acetone:hexane (1:1)) to give of the title compound (33%); TLC, R_f = 0.40 & 0.44, MeOH:CHCl₃ (1:9).

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₂₁ H ₃₀ F ₃ N ₃ O ₄ S: | C, 52.82; | H, 6.33; | N, 8.80 |
| Found: | C, 52.43; | H, 6.53; | N, 8.08 |

c. 3(RS)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = (2-thiophenyl)CH₂, R⁴ = H, A = CO, n = 1).

To a suspension of CrO₃ (0.84 g, 8.4 mmol) in dry CH₂Cl₂ (50 ml) was added dry pyridine (1.36 ml, 17 mmol), and the mixture stirred at room temperature for 30 min. To the resulting burgundy colored suspension was added 1 g of Celite® followed by the product from Example 61b (0.20 g, 0.42 mmol) in CH₂Cl₂ (5 ml). The mixture was stirred until TLC indicated all the alcohol was consumed. The mixture was then filtered through a pad of silica gel with methanol:chloroform (1:9) and the solvents removed from the filtrate under vacuum. The crude product was purified by preparative TLC (MeOH:CHCl₃ (5:95)) to afford the product (150 mg) as a white solid; HPLC, t_R = 4.18 & 5.65, Col A, H₂O:CH₃CN (60:40), FR = 2.0.

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₂₁ H ₂₈ F ₃ N ₃ O ₄ S.0.5H ₂ O: | C, 52.06; | H, 6.03; | N, 8.67 |
| Found: | C, 52.03; | H, 6.19; | N, 8.38 |

Example 62

3(RS)-(Phenylmethoxycarbonyl)-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = \emptyset CH₂, R⁴ = H, A = OCO, n = 1)

a. 2(RS),3(SR)-(Phenylmethoxycarbonyl)-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = \emptyset CH₂, R⁴ = H, A = OCO, n = 1).

Using the method of Example 20a, material prepared according to the procedure of Example 61a was allowed to react with 1.5 equivalents of benzyl chloroformate in one-fourth the amount of CHCl₃ used in the method of Example 20a to produce the title compound, isolated in 51% yield after purification by flash chromatography (acetone:hexane (1:4)); TLC, R_f = 0.38 & 0.43, acetone:hexane (40:60).

b. 3(RS)-(Phenylmethoxycarbonyl)-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = \emptyset CH₂, R⁴ = H, A = OCO, n = 1).

Using the method of Example 61c the product of Example 62a was oxidized to afford, after purification by flash chromatography (acetone: hexane (30:70)), the title product (64%); HPLC, t_R = 5.69 & 7.75, Col A, H₂O:CH₃CN (55:45), FR = 2.0.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| C ₂₃ H ₃₀ F ₃ N ₃ O ₅ * 0.80H ₂ O: | C, 55.26; | H, 6.37; | N, 8.40 |
| Found: | C, 55.10; | H, 6.19; | N, 8.77 |

Example 63

3(RS)-(Phenoxycarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide
(Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = \emptyset , R⁴ = H, A = OCO, n = 1)

a. 2(RS),3(SR)-(Phenoxycarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = \emptyset , R⁴ = H, A = OCO, n = 1).

Using the method of Example 20a, but using NMM instead of TEA, material prepared according to the procedure of Example 61a was allowed to react with 1.5 equivalents of phenyl chloroformate to produce the title compound, isolated in 18% yield after purification by preparative TLC (acetone:hexane (3:7)); TLC, R_f = 0.32 & 0.37, acetone:hexane (3:7).

b. 3(RS)-(Phenoxycarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = \emptyset , R⁴ = H, A = OCO, n = 1).

Using the method of Example 61c, the product of Example 63a was oxidized to afford, after purification by flash chromatography (EtOAc: hexane (1:9)), the title product (60%); HPLC, t_R = 4.57 & 6.51, Col A, H₂O:CH₃CN (55:45).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₂ H ₂₈ F ₃ N ₃ O ₅ : | C, 56.04; | H, 5.98; | N, 8.90 |
| Found: | C, 56.04; | H, 6.18; | N, 8.85 |

Example 64

3(RS)-[4-(1-Oxoethylamino)phenylsulfonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide
(Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = 4-(CH₃CONH) \emptyset , R⁴ = H, A = S(O₂), n = 1)

a. 2(RS),3(SR)-[4-(1-Oxoethylamino)phenylsulfonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = 4-(CH₃CONH) \emptyset , R⁴ = H, A = S(O₂), n = 1).

To a stirred solution of material prepared according to Example 3d (1.00 g, 2.72 mmol) and NMM (0.28 g, 0.30 ml, 2.80 mmol) in CH₂Cl₂ (50 ml) under N₂ was added 4-acetamidobenzenesulfonyl chloride (0.64 g, 2.72 mmol). After stirring the reaction mixture overnight at room temperature, the solution was washed (5% aq citric acid, brine), dried (Na₂SO₄), filtered, and concentrated to leave an orange syrup which was flash chromatographed over silica gel (350 g) (MeOH: CHCl₃ (7:93)) to give the title product (810 mg, 52.60%); TLC, R_f = 0.34 & 0.45, MeOH:CHCl₃ (7:93).

b. 3(RS)-[4-(1-Oxoethylamino)phenylsulfonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = 4-(CH₃CONH) \emptyset , R⁴ = H, A = S(O₂), n = 1).

Using the method of Example 31c, the product of Example 64a was oxidized to afford, after purification by flash chromatography (MeOH:CHCl₃ (5:95)), the title product (84%); HPLC, t_R = 3.22 & 4.58, Col A, CH₃CN:H₂O (40:60), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₄ H ₃₃ F ₃ N ₄ O ₆ S.H ₂ O: | C, 49.65; | H, 6.08; | N, 9.65 |
| Found: | C, 49.73; | H, 5.86; | N, 9.53 |

Example 65

3(RS)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = \emptyset CH₂OCONH(CH₂)₄, R³ = (CH₃)₃C, R⁴ = H, A = OCO, n = 1)

- 5 a. 2(RS),3(SR)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb R¹ = CH(CH₃)CH₃, R² = \emptyset CH₂OCONH(CH₂)₄, R³ = (CH₃)₃C, R⁴ = H, A = OCO, n = 1).

Using the method of Example 84b, N²-BOC-N⁶-CBZ-L-lysine was allowed to react with material
10 prepared by the method of Example 2b to provide, after purification by flash chromatography (gradient elution, MeOH:CHCl₃ (2.5:97.5) to (5:95)), the title product (73%); TLC, R_f = 0.57, MeOH:CHCl₃ (5:95).

- b. 3(RS)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = \emptyset CH₂OCONH(CH₂)₄, R³ = (CH₃)₃C, R⁴ = H, A = OCO, n = 1).
15

Using the method of Example 31c, the product of Example 65a was oxidized to afford, after purification by flash chromatography (gradient elution, MeOH: CHCl₃ (2.5:97.5) to (5:95)), the title product (65%); HPLC, t_R = 4.15 & 5.14, Col A, H₂O:CH₃CN (45:55), FR = 2.0.

20

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₃₀ H ₄₃ F ₃ N ₄ O ₇ .0.5H ₂ O: | C, 56.51; | H, 6.95; | N, 8.79 |
| Found: | C, 56.45; | H, 6.58; | N, 8.42 |

25

Example 66

30 3(RS)-[(2-Amino-5-chlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 2-NH₂-5-Cl- \emptyset , R⁴ = H, A = CO, n = 1)

- a. 2(RS),3(SR)-[(2-Amino-5-chlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 2-NH₂-5-Cl- \emptyset , R⁴ = H, A = CO, n = 1).

35

A solution of material prepared according to Example 3d (1 g, 2.7 mmol) in CH₂Cl₂ (50 ml) was treated with 5-chloroisotoic anhydride (0.54 g, 2.7 mmol) at room temperature and the mixture was stirred overnight before it was washed (5% aqueous NaHCO₃, brine), dried (Na₂SO₄), concentrated under vacuum, and purified by flash chromatography (MeOH:CHCl₃ (3:97)) to give the title product (1.4 g, 78%) as a white foam; TLC, R_f = 0.30 & 0.25, MeOH:CHCl₃ (5:95).

40

- b. 3(RS)-[(2-Amino-5-chlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)₂, R³ = 2-NH₂-5-Cl- \emptyset , R⁴ = H, A = CO, n = 1).

45 Using the method of Example 31c, the product of Example 66a was oxidized to afford, after purification by flash chromatography (MeOH:CHCl₃ (3:97)), the title product (76%); HPLC, t_R = 3.41 & 4.62, Col A, H₂O:CH₃CN (50:50), FR = 2.0.

50

| Analysis calculated for: | | | |
|---|-----------|----------|----------|
| C ₂₃ H ₃₀ F ₃ N ₄ O ₄ .H ₂ O: | C, 51.45; | H, 6.01; | N, 10.43 |
| Found: | C, 51.65; | H, 5.74; | N, 9.68 |

55 Example 67

3(RS)-[(4-Methoxyphenyl)carbonyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₃, R³ = 4-(CH₃O)- \emptyset , R⁴ = H, A = CO, n = 1)

a. 2(RS),3(SR)-(4-Methoxyphenylcarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$, $R^3 = 4-(\text{CH}_3\text{O})-\text{O}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

Using the method of Example 20a, material prepared according to the procedure of Example 61a was allowed to react with 4-methoxybenzoylchloride to provide the title compound, isolated in 34% yield after purification by flash chromatography (EtOAc:hexane (60:40)), TLC, $R_f = 0.71$ & 0.73 , MeOH:CHCl₃ (1:9).

10

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{23}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_5 \cdot 0.3\text{H}_2\text{O}$ | C, 56.04; | H, 6.67; | N, 8.52 |
| Found: | C, 56.06; | H, 6.60; | N, 8.14 |

b. 3(RS)-(4-Methoxyphenylcarbonyl)-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$, $R^3 = 4-(\text{CH}_3\text{O})-\text{O}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, except the alcohol was dissolved in five times the solvent, the product of Example 67a was oxidized to afford, after purification by preparative TLC (MeOH: CHCl₃ (1:9)), the title product (40%); HPLC, $t_R = 8.89$ & 11.75 , Col A, H₂O:CH₃CN (70:30), FR = 2.0.

20

25

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{23}\text{H}_{30}\text{F}_3\text{N}_3\text{O}_5 \cdot \text{H}_2\text{O}$ | C, 54.86; | H, 6.41; | N, 8.35 |
| Found: | C, 54.89; | H, 6.38; | N, 7.48 |

Example 68

30 3(RS)-[2-(Tricyclo[3.3.1.1^{3,7}]-dec-1-yl)ethoxycarbonyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$, $R^3 = (1\text{-adamantyl})-\text{CH}_2\text{CH}_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$)

a. 2(RS),3(SR)-[2-(Tricyclo[3.3.1.1^{3,7}]-dec-1-yl)ethoxycarbonyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$, $R^3 = (1\text{-adamantyl})-\text{CH}_2\text{CH}_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$).

Using the method of Example 34b, material prepared according to the procedure of Example 61a was allowed to react with material prepared according to Example 7a to provide the title compound, isolated in 42% yield after purification by flash chromatography (EtOAc:hexane (20:80), then (50:50)); TLC, $R_f = 0.33$ & 0.44 , MeOH:CHCl₃ (5:95).

b. 3(RS)-[2-(Tricyclo[3.3.1.1^{3,7}]-dec-1-yl)ethoxycarbonyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$, $R^3 = (1\text{-adamantyl})-\text{CH}_2\text{CH}_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$).

Using the method of Example 61c, the product of Example 68a was oxidized to afford, after purification by flash chromatography (Et₂O:hexane (50:50), then (90:10)), the title product (66%); HPLC, $t_R = 4.64$ & 5.63 , Col A, H₂O:CH₃CN (25:75), FR = 2.0.

50

55

| Analysis calculated for: | | |
|---|-----------|---------|
| $\text{C}_{28}\text{H}_{42}\text{F}_3\text{N}_3\text{O}_5 \cdot 0.15\text{H}_2\text{O}$ | C, 60.01; | H, 7.60 |
| Found: | C, 59.76; | H, 7.65 |

Example 69

3(RS)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = \emptyset S(O₂)NH(CH₂)₄, R³ = (CH₃)₃C, R⁴ = H, A = OCO, n = 1)

- a. 2(RS),3(SR)-N²-(1,1-Dimethylethoxycarbonyl)-L-lysyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = H₂N(CH₂)₄, R³ = (CH₃)₃C, R⁴ = H, A = OCO, n = 1).

To a solution of material prepared according to Example 65a (3.0 g, 4.8 mmol) in absolute EtOH (60 ml) was added 10% Pd on carbon (0.6 g). The resulting suspension was stirred overnight under an atmosphere (____ Pascals) of H₂. Additional 10% Pd on carbon (0.3 g) was added, and stirring was continued for several hours. The reaction was filtered through Celite® and concentrated under vacuum to give the product (2.48 g), which was used directly.

- b. 2(RS),3(SR)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH₄(CH₃)CH₃, R² = \emptyset S(O₂)NH(CH₂)₄, R³ = (CH₃)₃C, R⁴ = H, A = OCO, n = 1).

Using the method of Example 72b, except NMM was used instead of TEA, the product of Example 69a was treated with benzene sulfonyl chloride to produce the title product, purified by flash chromatography (CHCl₃:MeOH (95:5)), in 69% yield; TLC, R_f = 0.29, MeOH:CHCl₃ (95:5).

- c. 3(RS)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = \emptyset S(O₂)NH(CH₂)₄, R³ = (CH₃)₃C, R⁴ = H, A = OCO, n = 1).

Using the method of Example 31c, the product of Example 69b was oxidized to afford, after purification by flash chromatography (gradient elution, MeOH:CHCl₃ (0:100) to (2.5:97.5)), the title product (57%); HPLC, t_R = 7.48 & 9.11, Col A, CH₃CN:H₂O (1:1), FR = 1.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₈ H ₁₆ F ₃ N ₄ O ₇ S*H ₂ O: | C, 51.52; | H, 6.64; | N, 8.58 |
| Found: | C, 51.47; | H, 6.46; | N, 7.80 |

Example 70

3(RS)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-α-aminobutanoyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₃CH₂, R³ = 4-[CH₃CH₂OC(O)] \emptyset , R⁴ = H, A = NHCO, n = 1)

- a. 2(RS),3(SR)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH₃CH₂, R³ = 4-[CH₃CH₂OC(O)] \emptyset , R⁴ = H, A = NHCO, n = 1).

Using the method of Example 15a, material prepared according to the procedure of Example 61a was allowed to react with ethyl 4-iso-cyanatobenzoate to provide the title compound, isolated in 46% yield; TLC, R_f = 0.53, MeOH:CHCl₃ (5:95).

- b. 3(RS)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₃CH₂, R³ = 4-[CH₃CH₂OC(O)] \emptyset , R⁴ = H, A = NHCO, n = 1).

Using the method of Example 61c, the product of Example 70a was oxidized to afford, after purification by flash chromatography (CHCl₃:MeOH (97:3)), the title product (68%); HPLC, t_R = 6.35 & 8.70, Col A, H₂O:CH₃CN (60:40), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|----------|
| C ₂₅ H ₃₃ F ₃ N ₄ O ₆ ·0.5H ₂ O: | C, 54.44; | H, 6.21; | N, 10.15 |
| Found: | C, 54.76; | H, 6.13; | N, 10.27 |

Example 71

10 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₂, R³ = 4[HOC(O)] \emptyset , R⁴ = H, A = NHCO, n = 1)

15 Using the method of Example 14, material prepared according to the procedure of Example 70b was converted into the title product and isolated by flash chromatography on Baker pH 5.0 silica gel (CHCl₃:MeOH (97:3)) in 61% yield; HPLC, t_R = 3.68 & 4.69, Col A, H₂O:CH₃CN (3:1), FR = 2.0.

| Analysis calculated for: | | | |
|---|-----------|----------|----------|
| C ₂₃ H ₂₉ F ₃ N ₄ O ₆ ·H ₂ O: | C, 51.88; | H, 5.86; | N, 10.52 |
| Found: | C, 51.98; | H, 5.69; | N, 10.19 |

Example 72

25 3(RS)-N⁶-Phenylmethoxycarbonyl-N²-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₂)₄NHCOOCH₂ \emptyset , R³ = \emptyset , R⁴ = H, A = S(O₂), n = 1)

30 a. 2(RS),3(SR)-N⁶-Phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide trifluoroacetic acid salt (Formula IVb, R¹ = CH(CH₃)CH₃, R² = \emptyset CH₂OCONH(CH₂)₄-, R⁴ = H, n = 1).

35 To a solution of product prepared according to the procedure of Example 65a (2.75 g, 4.4 mmol) in CH₂Cl₂ (7 ml) was added TFA (10.4 g, 90 mmol), and the solution was stirred at room temperature for 1 hr. Toluene (10 ml) was added, and the reaction mixture was concentrated under vacuum to afford the title product (3.4 g) which was used without further purification.

40 b. 2(RS),3(SR)-N⁶-Phenylmethoxycarbonyl-N²-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = (CH₂)₄NHC(O)OCH₂ \emptyset , R³ = \emptyset , R⁴ = H, A = S(O₂), n = 1).

45 To a solution of the product of Example 72a (0.83 g, 1.3 mmol) in CH₂Cl₂ (6.5 ml) were added TEA (0.39 g, 3.9 mmol) and benzenesulfonyl chloride (0.25 g, 1.4 mmol), and the reaction mixture was stirred overnight at room temperature. After the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc. The EtOAc solution was filtered and concentrated under vacuum to a residue which was purified by flash chromatography (gradient elution, MeOH:CHCl₃ (2.5:97.5) to (5:95)) to give the title product (81%); TLC, R_f = 0.52, MeOH:CHCl₃ (5:95).

c. 3(RS)-N⁶-Phenylmethoxycarbonyl-N²-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₂)₄NHC(O)OCH₂ \emptyset , R³ = \emptyset , R⁴ = H, A = S(O₂), n = 1).

50 Using the method of Example 31c, the product of Example 72b was oxidized to afford, after purification by flash chromatography (gradient elution, CHCl₃ to CHCl₃:MeOH (97.5:2.5)), the title product (63%); HPLC, t_R = 5.0 & 6.3, Col A, CH₃CN:H₂O (3:2), FR = 1.0.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₃₁ H ₃₉ F ₃ N ₄ O ₇ ·S·H ₂ O: | C, 54.22; | H, 6.02; | N, 8.16 |
| Found: | C, 54.17; | H, 5.80; | N, 7.86 |

Example 73

3(RS)-[2-(2-Methoxyethoxy)ethoxycarbonyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$ -, $R^3 = \text{CH}_3\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$)

a. 2(RS),3(SR)-[2-(2-Methoxyethoxy)ethoxycarbonyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$ -, $R^3 = \text{CH}_3\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$).

Using the method of Example 34b, material prepared according to the procedure of Example 61a was allowed to react with material prepared according to the procedure of Example 19a to provide the title compound, isolated in 75% yield after purification by flash chromatography (gradient, acetone:hexane (1:9) to (7:3)), TLC, $R_f = 0.30$ & 0.35 , acetone:hexane (40:60).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{17}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_6 \cdot 0.5\text{H}_2\text{O}$: | C, 48.22; | H, 7.14; | N, 6.61 |
| Found: | C, 48.13; | H, 6.90; | N, 6.07 |

b. 3(RS)-[2-(2-Methoxyethoxy)ethoxycarbonyl]-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2$, $R^3 = \text{CH}_3\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$).

Using the method of Example 61c the product of Example 73a was oxidized to afford, after purification by flash chromatography (gradient elution, EtOAc:hexane (1:1) to EtOAc to acetone:EtOAc (1:9)), the title product (40%); HPLC, $t_R = 5.70$ & 8.95 , Col A, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (75:25), $\text{FR} = 2.0$.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{21}\text{H}_{34}\text{F}_3\text{N}_3\text{O}_7$: | C, 48.77; | H, 7.14; | N, 6.61 |
| Found: | C, 48.13; | H, 6.90; | N, 6.09 |

Example 74

3(RS)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$ -, $R^3 = \text{Z-H}_2\text{NC}(\text{O})\text{NHC}(\text{O})\text{CH}=\text{CH}$ -, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$)

a. 2(RS),3(SR)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$ -, $R^3 = \text{Z-H}_2\text{NC}(\text{O})\text{NHC}(\text{O})\text{CH}=\text{CH}$ -, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

Using the method of Example 21b, material prepared by the procedure of Example 3d was allowed to react with Z-4-aminocarbonylamino-4-oxo-2-butenic acid to provide the title compound, isolated in 26% yield after purification by flash chromatography ($\text{MeOH}:\text{CHCl}_3$ (5:95)); TLC, $R_f = 0.17$ & 0.25 , $\text{MeOH}:\text{CHCl}_3$ - (5:95).

b. 3(RS)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}_3(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$ -, $R^3 = \text{Z-H}_2\text{NC}(\text{O})\text{NHC}(\text{O})\text{CH}=\text{CH}$ -, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

Using the method of Example 31c, the product of Example 74a was oxidized to afford, after purification by flash chromatography ($\text{MeOH}:\text{CHCl}_3$ (4:96)), the title product (29%); HPLC, $t_R = 1.78$ & 2.45 , Col A, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (65:35), $\text{FR} = 2.0$.

| Analysis calculated for: | | | |
|---|-----------|----------|----------|
| $C_{21}H_{30}F_3N_5O_6 \cdot 1.5H_2O$: | C, 47.37; | H, 6.25; | N, 13.15 |
| Found: | C, 47.29; | H, 5.77; | N, 13.02 |

Example 75

3(RS)-Phenylaminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = \emptyset$, $R^4 = H$, $A = NHCO$, $n = 1$)

a. 2(RS),3(SR)-Phenylaminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = \emptyset$, $R^4 = H$, $A = NHCO$, $n = 1$).

Using the method of Example 15a, material prepared by the procedure of Example 3d was allowed to react with phenylisocyanate to provide the title compound, isolated in 62% yield after purification by flash chromatography (MeOH:CHCl₃ (2:98)); TLC, $R_f = 0.24$ & 0.32 , MeOH:CHCl₃ (2:98).

b. 3(RS)-Phenylaminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = \emptyset$, $R^4 = H$, $A = NHCO$, $n = 1$).

Using the method of Example 31c, the product of Example 75a was oxidized to afford, after purification by flash chromatography (MeOH:CHCl₃ (2:98)), the title product (75%); HPLC, $t_R = 5.70$ & 8.77 , Col A, H₂O:CH₃CN (60:40), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|----------|
| $C_{23}H_{31}F_3N_4O_4 \cdot 0.75H_2O$: | C, 55.47; | H, 6.58; | N, 11.25 |
| Found: | C, 55.46; | H, 6.50; | N, 10.72 |

Example 76

3(RS)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset CH_2-$, $R^3 = 4-[CH_3CH_2OC(O)]\emptyset$, $R^4 = H$, $A = NHCO$, $n = 1$)

a. 2(RS),3(SR)-1-Phenylmethoxycarbonyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIa, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset CH_2-$, $A = OCO$, $n = 1$).

Using the method of Example 2a, material prepared according to the method of Example 4 was allowed to react with CBZ-L-proline to provide the title compound (100%); TLC, $R_f = 0.37$ & 0.45 , MeOH:CH₂Cl₂ - (5:95).

b. 2(RS),3(SR)-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula IVa, $R^1 = CH(CH_3)CH_3$, $n = 1$).

Using the method of Example 2b, the product of Example 76a was converted into the title product (100%); TLC, $R_f = 0.73$ & 0.81 , MeOH:CH₂Cl₂, sat'd with NH₄OH (15:85).

c. 2(RS),3(SR)-Phenylmethoxycarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_2\emptyset$, $R^3 = \emptyset CH_2-$, $R^4 = H$, $A = OCO$, $n = 1$).

After DCC (2.27 g, 11.0 mmol) was added to a stirred solution of CBZ-L-phenylalanine (2.29 g, 10.0 mmol), HOBT (2.70 g, 17.6 mmol) and material prepared according to Example 76b (2.68 g, 10.0 mmol) in dry THF (45 ml) chilled to -17°C, the mixture was left at room temperature overnight, filtered, and concentrated to remove the THF before it was taken up in Et₂O and EtOAc. The resulting solution was washed (sat'd NaHCO₃ (2x), 1N HCl, brine), dried (MgSO₄), filtered, concentrated, and taken up in minimal

CH₂Cl₂. After N,N'-dicyclohexylurea was filtered, the solution was concentrated under vacuum, and dried under vacuum to provide the title compound in quantitative yield as a white foam; TLC, R_f = 0.37 & 0.45, MeOH:CH₂Cl₂ (5:95).

- 5 d. 2(RS),3(SR)-L-Phenylalanyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula IVb, R¹ = CH(CH₃)CH₃, R² = CH₂Ø, R⁴ = H, n = 1).

A mixture of the product of Example 76c (501.3 mg, 0.898 mmol) and 50%-water wet 10% Pd/C (50 mg) in absolute EtOH (17 ml) was stirred under hydrogen (1 atmosphere, 101,325 Pascals) overnight, filtered, concentrated and dried under vacuum to provide the title compound in quantitative yield; TLC, R_f = 0.14, MeOH: CH₂Cl₂ (5:95); R_f = 0.43 & 0.48 MeOH: NH₄ OH satd CH₂Cl₂ (5:95).

- 10 e. 2(RS),3(SR)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIb, R¹ = CH(CH₃)CH₃, R² = ØCH₂-, R³ = 4-[CH₃CH₂OC(O)]Ø-, R⁴ = H, A = NHCO, n = 1).

Using the method of Example 15a material prepared by the procedure of Example 76d was allowed to react with ethyl 4-isocyanatobenzoate to provide the title compound, isolated in 95% yield; TLC; R_f = 0.21 & 0.26, MeOH:CH₂Cl₂ (5:95).

- 20 f. 3(RS)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = ØCH₂-, R³ = 4-[CH₃CH₂OC(O)]Ø-, R⁴ = H, A = NHCO, n = 1).

25 Using the method of Example 61c, the product of Example 76e was oxidized to afford, after purification by flash chromatography (gradient elution, Et₂O: pentane (11:1) to Et₂O), the title product (94%); HPLC, t_R = 10.26 & 13.52, Col A, CH₃CN:H₂O (45:55), FR = 2.0.

30

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₃₀ H ₃₅ F ₃ N ₄ O ₆ · 1.24H ₂ O: | C, 57.47; | H, 6.03; | N, 8.94 |
| Found: | C, 57.43; | H, 6.02; | N, 8.97 |

35 Example 77

3(RS)-[[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[1-naphthyl-S(O₂)NHC(O)]Ø, R⁴ = H, A = NHCO, n = 1)

- 40 a. 1-Naphthalene sulfonamide.

Ammonia was passed (for 5 min) into a stirred solution of 1-naphthalenesulfonyl chloride (5.0 g, 22 mmol) and anhydrous Et₂O (400 ml) at -78°. The resulting mixture was stirred at -78° for 1 hr, allowed to warm to room temperature, and stirred overnight. The Et₂O was removed under vacuum to leave a white powder which was washed with water and dried under vacuum to give 3.2 g (70%) of the title compound as a white powder, m.p. 152-153° C.

- 50 b. 3(RS)-[[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[1-naphthyl-S(O₂)NHC(O)]Ø, R⁴ = H, A = NHCO, n = 1).

1-Naphthalene sulfonamide, prepared according to Example 77a (0.64 g, 3.09 mmol), was added to a stirred solution of material prepared according to Example 16 (1.5 g, 2.84 mmol). DMAP (0.38 g, 3.1 mmol), WSCDI (0.59 g, 3.08 mmol) and dry CH₂Cl₂ (40 ml) under nitrogen at room temperature. The resulting reaction mixture was stirred at room temperature overnight before it was washed (1N HCl), dried (MgSO₄), and filtered. The filtrate was concentrated under vacuum to a gummy residue which was purified by flash chromatography, (CH₂Cl₂ then CH₂Cl₂:MeOH:AcOH (98:1.9: 0.1) to give 0.76 g (36%) of the title compound

as a white powder; HPLC, $t_R = 10.08$ & 16.38 , Col A, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (30:70), $\text{FR} = 2.5$.

5

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{34}\text{H}_{39}\text{F}_3\text{N}_5\text{O}_7\text{S}\cdot\text{O}_2\text{H}_2\text{O}$ | C, 54.25; | H, 5.49; | N, 9.30 |
| Found: | C, 54.56; | H, 5.68; | N, 8.85 |

10 Example 78

3(RS)-N²-(4-Hydroxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₂)₄NHC(O)OCH₂Ø, R³ = 4-[HOC(O)]Ø, R⁴ = H, A = NHCO, n = 1)

- 15 a. 2(RS),3(SR)-N²-(4-Ethoxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = (CH₂)₄NHC(O)-OCH₂Ø, R³ = 4-[EtOC(O)]Ø, R⁴ = H, A = NHCO, n = 1).

20 Using the method of Example 15a, material prepared by the procedure of Example 72a was allowed to react with ethyl 4-isocyanatobenzoate to provide the title compound, isolated in 95% yield after purification by flash chromatography (gradient elution, CHCl_3 to $\text{MeOH}:\text{CHCl}_3$ (2:98), then (5:95)); TLC, $R_f = 0.41$ $\text{MeOH}:\text{CHCl}_3$ (2.5:97.5).

- 25 b. 3(RS)-N²-(4-Ethoxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₂)₄NHC(O)OCH₂Ø, R³ = 4-[EtOC(O)]Ø, R⁴ = H, A = NHCO, n = 1).

30 Using the method of Example 31c, the product of Example 78a was oxidized to afford, after purification by flash chromatography (gradient elution, CHCl_3 to $\text{MeOH}:\text{CHCl}_3$ (2.5:97.5) to (5:95)), the title product (77%); TLC, $R_f = 0.48$, $\text{MeOH}:\text{CHCl}_3$ (2.5:97.5).

- 35 c. 3(RS)-N²-(4-Hydroxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₂)₄NHC(O)OCH₂Ø, R³ = 4-[HOC(O)]Ø, R⁴ = H, A = NHCO, n = 1).

Using the method of Example 14, material prepared according to the procedure of Example 78b was converted into the title product and isolated in 85% yield; HPLC, $t_R = 4.71$ & 6.76 , Col A, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (40:60), $\text{FR} = 2.5$.

40

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{33}\text{H}_{40}\text{F}_3\text{N}_5\text{O}_8\cdot 1.5\text{H}_2\text{O}$ | C, 55.15; | H, 6.03; | N, 9.74 |
| Found: | C, 54.90; | H, 5.92; | N, 9.29 |

45

Example 79

3(RS)-(4-Hydroxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[HOC(O)]Ø, R⁴ = H, A = CO, n = 1)

50

Using the method of Example 14, material prepared according to the procedure of Example 84c was converted into the title product and isolated in 72% yield; HPLC, $t_R = 3.48$ & 5.31 , Col A, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (3:1), $\text{FR} = 2.0$.

55

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $C_{24}H_{30}F_3N_3O_6 \cdot 1.0H_2O$: | C, 54.23; | H, 6.07; | N, 7.91 |
| Found: | C, 54.46; | H, 6.05; | N, 7.69 |

5

Example 80

10 3(RS)-Phenylsulfonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_3CH_2-$, $R^3 = \emptyset$, $R^4 = H$, $A = S(O_2)$, $n = 1$)

a. 2(RS),3(SR)-Phenylsulfonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_3CH_2-$, $R^3 = \emptyset$, $R^4 = H$, $A = S(O_2)$, $n = 1$).

15 NMM (0.24 g, 2.4 mmol) and benzenesulfonyl chloride (0.21 g, 1.2 mmol) were added to a solution of material prepared according to Example 61a (0.5 g, 1.1 mmol) in CH_2Cl_2 (5 ml), and the reaction was stirred overnight at room temperature. The reaction was concentrated under vacuum; the residue was taken up in EtOAc and filtered; and the filtrate concentrated under vacuum to give the crude product. The product was partially purified by flash chromatography (gradient, MeOH: $CHCl_3$ (2.5:97.5) to (5:95)) and finally
20 purified by flash chromatography (gradient, Et₂O:hexane (80: 20) to Et₂O:hexane (90:10) to Et₂O) to give the title product (0.118 g); TLC, $R_f = 0.33$, Et₂O.

b. 3(RS)-Phenylsulfonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_3CH_2-$, $R^3 = \emptyset$, $R^4 = H$, $A = S(O_2)$, $n = 1$).

25

Using the method of Example 31c, the product of Example 80a was oxidized to afford, after purification by flash chromatography (gradient, MeOH: $CHCl_3$ (0:100) to (2:98) to (5:95)), the title product (42%); HPLC, $t_R = 4.97$ & 6.17, Col A, H₂O: CH_3CN (1:1), FR = 1.0.

30

| Analysis calculated for: | | | |
|---------------------------------------|-----------|----------|---------|
| $C_{21}H_{28}F_3N_3O_5S \cdot H_2O$: | C, 49.50; | H, 5.93; | N, 8.25 |
| Found: | C, 49.70; | H, 6.24; | N, 7.67 |

35

Example 81

40 3(RS)-[1-(Ethoxycarbonyl)cyclopent-1-yl]carbonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_3CH_2-$, $R^3 = 1-[CH_3CH_2OC(O)]$ cyclopent-1-yl, $R^4 = H$, $A = CO$, $n = 1$)

a. 1-(Ethoxycarbonyl)cyclopentanecarboxylic acid.

45 To a solution of diethyl 1,1-cyclopentane dicarboxylate (2.5 g, 11.68 mol) in EtOH (10 ml) was added dropwise a solution of KOH (654 mg, 11.68 mmol) in EtOH (10 ml) over $\frac{1}{2}$ hour. The resulting mixture was stirred at room temperature for 96 hr, concentrated under vacuum, and partitioned between H₂O and EtOAc. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc. The EtOAc extracts were washed (brine), dried (Na₂SO₄), filtered, and concentrated under vacuum to give the product (1.73 g) as a
50 clear oil.

b. 2(RS),3(SR)-[1-(Ethoxycarbonyl)cyclopent-1-yl]carbonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = CH(CH_3)CH_3$, $R^2 = CH_3CH_2-$, $R^3 = 1-[CH_3CH_2OC(O)]$ cyclopent-1-yl, $R^4 = H$, $A = CO$, $n = 1$).

55

Using the method of Example 50a with the following ratios of reagents to one equivalent of the product prepared according to Example 81a: HOBT (3.3 equivalents), DCC (1.65 equivalents), TEA (1.5 equivalents) and material prepared according to the procedure of Example 61a (1.0 equivalent), and omitting the citric

acid wash, the title product was prepared, isolated by suction chromatography (gradient elution, Et₂O:hexane (1:1) to Et₂O) in 46% yield; TLC, R_f = 0.47, MeOH:CHCl₃ (5:95).

5

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₄ H ₃₈ F ₃ N ₃ O ₆ : | C, 55.27; | H, 7.34; | N, 8.06 |
| Found: | C, 54.74; | H, 5.93; | N, 7.88 |

10

c. 3(RS)-[1-(Ethoxycarbonyl)cyclopent-1-yl]carbonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₂, R³ = 1-[CH₂CH₂OC(O)]-cyclopent-1-yl, R⁴ = H, A = CO, n = 1).

15

Using the method of Example 33c, the product of Example 81b was oxidized to afford, after purification by flash chromatography (acetone:hexane (1:4)), the title product (37%); HPLC, t_R = 6.68 & 8.31, Col A, H₂O:CH₃CN (70:30), FR = 2.0.

20

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₄ H ₃₆ F ₃ N ₃ O ₆ .1.1H ₂ O: | C, 53.44; | H, 7.13; | N, 7.80 |
| Found: | C, 53.48; | H, 6.97; | N, 7.60 |

25 Example 82

3(RS)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = CH₂CH₂, R³ = 1-adamantyl, R⁴ = H, A = S(O₂), n = 1)

30

a. 1-Adamantane sulfinyl chloride.

35

Aluminum trichloride (40 g, 3 mol) was added slowly to thionyl chloride (200 ml, 2.7 mol), and the mixture was cooled to -20°. Adamantane was added in portions over 2½ hrs, and the resulting mixture was stirred 1 hr and allowed to warm to room temperature. After the thionyl chloride was removed under vacuum, the residue was diluted with CCl₄, and the aluminum trichloride was decomposed with ice and water. The layers were separated; and the organic layer was washed (brine), dried (Na₂SO₄), filtered, and concentrated under vacuum. The residue was distilled under vacuum (1 torr, 133.3 Pascals) with a vigreux column to give the product (28.8 g; bp 118-128°) as a waxy solid; TLC, R_f = 0.6-0.4, EtOAc:hexanes (15:85).

40

b. 2(RS),3(SR)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH₂CH₂, R³ = 1-adamantyl, R⁴ = H, A = S(O), n = 1).

45

Using the method of Example 20a, material prepared according to the procedure of Example 61a was allowed to react with material prepared according to Example 82a to provide the title compound, isolated in 61% yield after purification by suction flash chromatography (gradient, Et₂O:EtOAc (1:1) to EtOAc); TLC, R_f = 0.53, MeOH:CHCl₃ (5:95).

50

| Analysis calculated for: | | |
|--|-----------|---------|
| C ₂₅ H ₄₀ F ₃ N ₃ O ₄ S.0.45H ₂ O: | C, 55.22; | H, 7.58 |
| Found: | C, 55.05; | H, 7.57 |

55

c. 2(RS),3(SR)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH₂CH₂, R³ = 1-adamantyl, R⁴ = H, A = S(O₂), n = 1).

To a solution of the product of Example 82b (277 mg, 0.515 mmol) in acetone (25 ml) at reflux was added a satd acetone solution of KMnO_4 (60 ml) dropwise over 1 hr. This was stirred 15 min at reflux, cooled, filtered through Celite®, and concentrated under vacuum. The crude product was purified by flash chromatography ($\text{EtOAc}:\text{Et}_2\text{O}$ (4:6)) to give the title product (180 mg) as a solid; TLC, $R_f=0.67$ & 0.70, MeOH: CHCl_3 (1:9).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{25}\text{H}_{40}\text{F}_3\text{N}_3\text{O}_5\text{S}$: | C, 54.43; | N, 7.31; | N, 7.62 |
| Found: | C, 54.49; | N, 7.33; | N, 7.39 |

d. 3(RS)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2-$, $R^3 = 1\text{-adamantyl}$, $R^4 = \text{H}$, $A = \text{S}(\text{O}_2)$, $n = 1$).

Using the method of Example 33c, the product of Example 82c was oxidized to afford, after purification by flash chromatography (acetone:hexanes (15: 85)), the title product (40%); HPLC, $t_R = 6.27$ & 8.29, Col A, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (1:1), $FA = 2.0$.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{25}\text{H}_{38}\text{F}_3\text{N}_3\text{O}_5\text{S}\cdot 0.5\text{H}_2\text{O}$: | C, 53.75; | H, 7.04; | N, 7.32 |
| Found: | C, 53.91; | H, 7.11; | N, 6.97 |

Example 83

3(RS)-[1-(Hydroxycarbonyl)cyclopent-1-yl]carbonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}_3\text{CH}_2-$, $R^3 = 1\text{-[HOC(O)]cyclopent-1-yl}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$)

Using the method of Example 14, material prepared according to the procedure of Example 81c was converted into the title product and isolated in 79% yield; HPLC, $t_R = 3.74$ & 4.92, Col A, $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (3:1), $FA = 2.0$.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{22}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_6\cdot 0.35\text{H}_2\text{O}$: | C, 53.08; | H, 6.62; | N, 8.44 |
| Found: | C, 53.04; | H, 6.58; | N, 8.16 |

Example 84

3(RS)-(4-Methoxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4\text{-[CH}_3\text{OC(O)]}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$)

a. 4-Methoxycarbonylbenzenecarboxylic acid.

Concentrated sulfuric acid (277.5 ml, 5.2 mol) was added dropwise over $\frac{1}{2}$ hr to a stirred solution of chromium (VI) oxide (299.25 g, 2.99 mol) and water (925 ml) at 0°. The resulting solution was added dropwise over 1 hr to a stirred solution of methyl-4-(hydroxymethyl)benzoate (92.5 g, 0.564 mol) and acetone (4.6 l) at 0°. The reaction mixture was allowed to warm to room temperature and stirred overnight. The supernatant was decanted before the black tar-like residue was extracted with acetone. The decanted supernatant and acetone extracts were combined and concentrated under vacuum to leave a dark brown residue which was triturated with cold water (4 liter). The precipitate which formed was collected, washed three times with water (1 liter), and dried to give 94.6 g (94%) of the title compound as white crystals, m.p. 218-221° C.

b. 2(RS),3(SR)-(4-Methoxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-}[\text{CH}_3\text{OC}(\text{O})]\emptyset$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

WSCDI (10.27 g, 53.6 mmol) was added to a stirred solution of a compound prepared according to Example 3d (17.54 g, 47.8 mmol), the product of Example 84a (8.6 g, 47.8 mmol), HOBT (12.86 g, 95.3 mmol) and dry THF (400 ml) at 0° under nitrogen. The resulting reaction mixture was stirred at 0° for 1 hr; then it was allowed to come to room temperature and to stir overnight. The THF was removed under vacuum to leave an oily residue which was dissolved in EtOAc. The EtOAc solution was washed (1N HCl, satd aq, NaHCO_3 , and brine), dried (MgSO_4), filtered, and concentrated under vacuum to give 24.45 g of the crude product as a dry white foam. Purification by flash chromatography ($\text{CHCl}_3\text{:MeOH}$ (97:3)) produced the title compound (79%); HPLC, $t_R = 4.62$ & 5.80, Col A, $\text{H}_2\text{O:CH}_3\text{CN}$ (55:45); FR = 3.0.

c. 3(RS)-(4-Methoxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-}[\text{CH}_3\text{OC}(\text{O})]\emptyset$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

Using the method of Example 31c, the product of Example 84b was oxidized to afford, after purification by flash chromatography ($\text{CHCl}_3\text{:MeOH}$ (98:2)), the title product (69%); HPLC, $t_R = 4.51$ & 6.82, Col A, $\text{H}_2\text{O:CH}_3\text{CN}$ (55:45), FA = 2.0.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| $\text{C}_{25}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_6 \cdot 0.5\text{H}_2\text{O}$ | C, 55.96; | H, 6.19; | N, 7.83 |
| Found: | C, 55.90; | H, 6.30; | N, 7.93 |

d. 3(RS)-(4-Methoxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = 4\text{-}(\text{CH}_3\text{OCO})\emptyset$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

A preferred method employing the oxidation described in D. B. Dess and J. C. Martin, J. Org. Chem., 48, 4155-4156(1983) for the preparation of the title compound is as follows: To a stirred solution of Dess-Martin periodinane (6.76 g, 15.96 mmol) and a product prepared using the method of Example 84b (6.49 g, 12.25 mmol) in dry CH_2Cl_2 (80 ml) under nitrogen was added TFA (1.82 g, 1.23 ml, 15.96 mmol). After the reaction mixture had been stirred overnight at room temperature, Et_2O (~240-400ml) added, and the mixture was poured into an aq solution of satd NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (17.63 g, 111.51 mmol). After 15 min of stirring, the organic layer was separated, washed (satd NaHCO_3 , brine), dried (Na_2SO_4), filtered, and concentrated to give the title product as a white foam (6.42 g, 99.4%); TLC, $R_f = 0.67$ & 0.76; MeOH:CHCl_3 (3:97); HPLC, $t_R = 4.64$ & 6.84, Col A, $\text{H}_2\text{O:CH}_3\text{CN}$ (60:40), FR = 2.0.

Example 85

3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \emptyset\text{CH}_2$, $R^3 = 4\text{-}[\text{HOC}(\text{O})]\emptyset$, $R^4 = \text{H}$, $A = \text{NHCO}$, $n = 1$)

Using the method of Example 14, material prepared according to the procedure of Example 76f was converted into the title product and isolated by flash chromatography (gradient, $\text{MeOH:CH}_2\text{Cl}_2$ (4:96) to (10:90)) in 48% yield; HPLC, $t_R = 5.52$ & 8.12, Col A, $\text{CH}_3\text{CN:H}_2\text{O}$ (35:65), FR = 2.0.

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| $\text{C}_{28}\text{H}_{31}\text{F}_3\text{N}_4\text{O}_5 \cdot \text{H}_2\text{O}$ | C, 56.56; | H, 5.59; | N, 9.42 |
| Found: | C, 56.58; | H, 5.59; | N, 9.22 |

Example 86

3(RS)-(4-Methoxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-}[\text{CH}_3\text{OC}(\text{O})]\emptyset\text{CH}_2$, $R^4 = \text{H}$, $A = \text{OCO}$,

n = 1)

a. (4-Methoxycarbonylphenyl)methyl 4-nitrophenyl carbonate.

5 Using the method of Example 7a, but omitting the pH 7.0 wash, methyl 4-hydroxymethylbenzoate was converted into the title compound which was isolated by trituration with hexanes, washed with hexanes:EtOAc (1:1), and dried under vacuum to provide a 50% yield; TLC, $R_f = 0.75$ EtOAc:hexane (1:1).

b. 2(RS),3(SR)-(4-Methoxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methyl-
10 penty)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-}[\text{CH}_2\text{OC}(\text{O})]\text{CH}_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$).

Using the method of Example 7b, material prepared by the procedure of Example 3d was allowed to react with the product of Example 86a to provide the title compound, which was isolated in 48% yield after
15 purification by flash chromatography (acetone: hexanes (2:3)), TLC, $R_f = 0.63$ & 0.68 , MeOH: CHCl_3 (1:9).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{26}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_7$: | C, 55.81; | H, 6.48; | N, 7.51 |
| Found: | C, 55.54; | H, 6.39; | N, 7.29 |

c. 3(RS)-(4-Methoxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopenty)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-}[\text{CH}_2\text{OC}(\text{O})]\text{CH}_2$, $R^4 = \text{H}$, $A = \text{OCO}$,
25 $n = 1$).

Using the method of Example 33c, the product of Example 86b was oxidized to afford, after purification by preparative TLC (EtOAc: Et_2O (3:2)), the title product (10%); HPLC, $t_R = 4.32$ & 6.44 , $\text{H}_2\text{O}:\text{CH}_3\text{CH}$ (1:1),
30 $\text{FR} = 2.0$.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{26}\text{H}_{34}\text{F}_3\text{N}_3\text{O}_7 \cdot 0.65\text{H}_2\text{O}$: | C, 54.86; | H, 6.25; | N, 7.38 |
| Found: | C, 54.87; | H, 6.25; | N, 7.05 |

Example 87

40 3(RS)-[E-3-(4-Ethoxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopenty)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = \text{E-4-}[\text{CH}_2\text{CH}_2\text{O-C}(\text{O})]\text{CH}=\text{CH}$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$)

a. Ethyl 4-formylbenzoate.

45 A mixture of 4-formylbenzoic acid (25 g) conc sulfuric acid (2 ml) and EtOH (19.5 ml) was refluxed gently for 5 days in 100 ml of 1,2-dichloroethane. The solvent was then stripped, and Et_2O was added to the residue. The Et_2O solution was washed (satd aq NaHCO_3) dried (Na_2SO_4), filtered, and evaporated. Bulb to bulb distillation afforded 20.1 g (68%) of the title ester as a clear liquid, bp $145\text{-}150^\circ$ (2900 Pascals,
50 22 torr).

b. E-(4-Ethoxycarbonyl)benzenepropenoic acid.

55 A mixture of the product of Example 87a (8.9 g), malonic acid (10.4 g), and piperidine (1 ml) in 25 ml of pyridine was heated on a steam bath for 3 hr. After the solvent was evaporated and the residue slurried in 200 ml of water, the pH was adjusted to 6 with acetic acid. The precipitate was collected and air dried. Crystallization of the material from EtOH gave 10.1 g (92%) of the title acid as sparkling white crystals, mp $220.5\text{-}221^\circ$.

c. 2(RS),3(SR)-[E-3-(4-Ethoxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = \text{E}-[4-\text{CH}_3\text{CH}_2\text{O}-\text{C}(\text{O})]-\text{CH}=\text{CH}$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

5 Using the method of Example 32a, material prepared by the procedure of Example 3d was allowed to react with the product of Example 87b to provide the title compound, isolated in 88% yield; TLC, $R_f = 0.14$ & 0.18, MeOH:CH₂Cl₂ (5:95).

d. 3(RS)-[E-3-(4-Ethoxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = \text{E}-[4-\text{CH}_3\text{CH}_2\text{OC}(\text{O})]\text{CH}=\text{CH}$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 87c was oxidized to afford, after purification by flash chromatography (MeOH: CH₂Cl₂ (2:98)), the title product (65%); TLC, $R_f = 0.23$, MeOH:CH₂Cl₂ - (5:95).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{28}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_6$: | C, 59.25; | H, 6.39; | N, 7.40 |
| Found: | C, 59.14; | H, 6.75; | N, 7.21 |

Example 88

25 3(RS)-(2-Ethoxycarbonylphenyl)aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 2-[\text{CH}_3\text{CH}_2\text{OC}(\text{O})]\text{CH}=\text{CH}$, $R^4 = \text{H}$, $\text{A} = \text{NHCO}$, $n = 1$).

30 a. 2(RS),3(SR)-(2-Ethoxycarbonylphenyl)aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 2-[\text{CH}_3\text{CH}_2\text{OC}(\text{O})]\text{CH}=\text{CH}$, $R^4 = \text{H}$, $\text{A} = \text{NHCO}$, $n = 1$).

Using the method of Example 15a, material prepared by the procedure of Example 3d was allowed to react with ethyl 2-isocyanatobenzoate to provide the title compound, which was isolated in 66% yield after purification by flash chromatography (EtOAc: hexane (60:40)); TLC, $R_f = 0.48$ & 0.57, MeOH:CHCl₃ (5:95).

b. 3(RS)-(2-Ethoxycarbonylphenyl)aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^3 = 2-[(\text{CH}_3\text{CH}_2\text{OCO})\text{CH}=\text{CH}]$, $R^4 = \text{H}$, $\text{A} = \text{NHCO}$, $n = 1$).

40 A modification of the procedure of Example 54b was done using the indicated ratios of the product of Example 88a (1 equivalent), oxalyl chloride (2 equivalents), DMSO (4 equivalents) with the reaction mixture cooled to -45° for these above-listed additions and warmed to -20° for addition of the TEA (instead of diisopropylethylamine). The work up included washing (1N HCl, satd aq NaHCO₃, 10% aq NaOCl, brine). The title product was obtained after purification by flash chromatography (Et₂O:hexane (4:1)) in 74% yield, HPLC, $t_R = 6.95$ & 10.46, Col A, CH₃CN:H₂O (35:65), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{26}\text{H}_{35}\text{F}_3\text{N}_4\text{O}_6 \cdot 0.75 \text{H}_2\text{O}$: | C, 54.78; | H, 6.45; | N, 9.83 |
| Found: | C, 54.73; | H, 6.34; | N, 9.51 |

Example 89

55 3(RS)-4-[(4-Nitrophenyl)sulfonylaminocarbonyl]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4-[(4-\text{NO}_2)\text{S}(\text{O}_2)\text{NHCO}]\text{CH}=\text{CH}$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

4-Nitrobenzene sulfonamide (0.196 g, 0.97 mmol) was added to a stirred solution of the product of Example 79 (0.5 g, 0.97 mmol), DMAP (0.12 g, 0.97 mmol), DCC (0.22 g, 0.91 mmol), and dry CH_2Cl_2 (30 ml) under nitrogen at room temperature. The resulting mixture was stirred overnight at room temperature and filtered. The filtrate was washed (1N HCl), dried (MgSO_4), filtered, and concentrated under vacuum to a yellow residue which was purified by flash chromatography, (CHCl_3 :MeOH:AcOH (90:9.8:0.2)) to give 0.29 g (43%) of the title compound as a white powder; HPLC, t_R = 4.26 & 8.42, Col A, H_2O : CH_3CN (4:1), FR = 2.0.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{30}\text{H}_{34}\text{F}_3\text{N}_5\text{O}_9 \cdot \text{H}_2\text{O}$ | C, 50.34; | H, 5.06; | N, 9.78 |
| Found: | C, 50.03; | H, 4.92; | N, 9.43 |

Example 90

3(RS)-Phenylmethoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide phenylmethyl ester (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = -(\text{CH}_2)_2\text{C}(\text{O})\text{OCH}_2\emptyset$, $\text{R}^3 = \emptyset\text{CH}_2-$, $\text{R}^4 = \text{H}$, $\text{A} = \text{OCO}$, $n = 1$)

a. 2(RS),3(SR)-Phenylmethoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = (\text{CH}_2)_2\text{C}(\text{O})\text{OCH}_2\emptyset$, $\text{R}^3 = \emptyset\text{CH}_2-$, $\text{R}^4 = \text{H}$, $\text{A} = \text{OCO}$, $n = 1$).

Using the method of Example 84b, CBZ-glutamic acid gamma-benzylester was allowed to react with material prepared according to the method of Example 2b to provide the title compound, isolated in 64% yield after purification by flash chromatography (gradient elution, hexane:Et₂O (1:3) to Et₂O); TLC, R_f = 0.61, Et₂O.

b. 3(RS)-Phenylmethoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide phenylmethyl ester (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = (\text{CH}_2)_2\text{C}(\text{O})\text{OCH}_2\emptyset$, $\text{R}^3 = \emptyset\text{CH}_2-$, $\text{R}^4 = \text{H}$, $\text{A} = \text{OCO}$, $n = 1$).

Using the method of Example 54b, the product of Example 90a was oxidized to afford, after purification by flash chromatography (gradient, hexane:Et₂O (2:8) to (1:9)), the title product (30%); HPLC, t_R = 6.12 & 8.48, Col A, CH_3CN : H_2O (1:1), FR = 3.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{31}\text{H}_{36}\text{F}_3\text{N}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$ | C, 56.78; | H, 6.15; | N, 6.41 |
| Found: | C, 56.98; | H, 5.74; | N, 6.12 |

Example 91

3S(or R)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = (\text{CH}_3)_2\text{CH}-$, $\text{R}^3 = 1\text{-adamantyl}$, $\text{R}^4 = \text{H}$, $\text{A} = \text{S}(\text{O}_2)$, $n = 1$)

a. 2(RS),3(SR)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfinyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = (\text{CH}_3)_2\text{CH}$, $\text{R}^3 = 1\text{-adamantyl}$, $\text{R}^4 = \text{H}$, $\text{A} = \text{S}(\text{O})$, $n = 1$).

Using the method of Example 20a, material prepared by the procedure of Example 3d was allowed to react with product from Example 82a to provide the title compound which was isolated by flash chromatography (EtOAc:Et₂O (2:3)); TLC, R_f = 0.75, MeOH: CHCl_3 (1:9).

b. 2(RS),3(SR)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = (\text{CH}_3)_2\text{CH}$, $\text{R}^3 = 1\text{-adamantyl}$, $\text{R}^4 = \text{H}$, $\text{A} = \text{S}(\text{O}_2)$, $n = 1$).

Using the method of Example 82c, the product of Example 91a was converted into the title product, isolated in 60% yield after purification by flash chromatography (EtOAc:hexane (2:3)); TLC, R_f = 0.29 & 0.35.

EtOAc:hexane (1:1).

| | | | | |
|---|--|-----------|----------|---------|
| 5 | Analysis calculated for: | | | |
| | $C_{26}H_{42}F_3N_3O_5S \cdot 2.5H_2O$: | C, 51.13; | H, 7.75; | N, 6.88 |
| | Found: | C, 51.12; | H, 7.03; | N, 6.40 |

- 10 c. 3S(or R)-Tricyclo[3.3.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = 1$ -adamantyl, $R^4 = H$, $A = S(O_2)$, $n = 1$).

Using the method of Example 33c, the product of Example 91b was oxidized to afford, after purification by flash chromatography (EtOAc:hexane (1:1)), the title product (57%) as one substantially pure isomer; HPLC, $t_R = 3.01$, Col A, $H_2O:CH_3CN$ (45:55), $FR = 2.0$.

| | | | |
|----|--|-----------|---------|
| 20 | Analysis calculated for: | | |
| | $C_{26}H_{40}F_3N_3O_5S \cdot 0.4H_2O$: | C, 54.70; | H, 7.20 |
| | Found: | C, 54.89; | H, 7.17 |

Example 92

- 25 3(RS)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset$, $R^3 = 4-[CH_3CH_2O-C(O)]\emptyset$, $R^4 = H$, $A = NHCO$, $n = 1$)

- a. 2(RS),3(SR)-Phenylmethoxycarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset$, $R^3 = \emptyset CH_2-$, $R^4 = H$, $A = OCO$, $n = 1$).

Using the method of Example 50a, material prepared according to the procedure of Example 76b was allowed to react with CBZ-L-phenyl-glycine to provide, after purification by flash chromatography (MeOH:CH₂Cl₂ (5:95)), the title product (95%); TLC, $R_f = 0.13$ & 0.19 , MeOH:CH₂Cl₂ (5:95).

- 35 b. 2(RS),3(SR)-L-Phenylglycyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula IVb, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset$, $R^4 = H$, $n = 1$).

Using the method of Example 2b, material prepared according to the procedure of Example 92a was converted into the title product in 100% yield.

- 40 c. 2(RS),3(SR)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset$, $R^3 = 4-[CH_3CH_2OC(O)]\emptyset$, $R^4 = H$, $A = NHCO$, $n = 1$).

45 Using the method of Example 15a, material prepared according to the procedure of Example 92b was allowed to react with ethyl 4-isocyanatobenzoate to provide the title product (86%); TLC, $R_f = 0.24$ & 0.27 , MeOH:Et₂O (1:99).

- 50 d. 3(RS)-(4-Ethoxycarbonylphenyl)aminocarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset$, $R^3 = 4-[CH_3CH_2OC(O)]\emptyset$, $R^4 = H$, $A = NHCO$, $n = 1$).

Using the method of Example 31c, the product of Example 92c was oxidized to afford, after purification by flash chromatography (gradient, Et₂O to CH₃CN: Et₂O (1:99)), the title product (82%); HPLC, $t_R = 8.88$ & 10.82 , Col A, $CH_3CN:H_2O$ (45:55); $FR = 2.0$.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $C_{29}H_{33}F_3N_4O_6 \cdot 0.64H_2O$: | C, 56.77; | H, 5.80; | N, 8.75 |
| Found: | C, 56.62; | H, 5.78; | N, 8.78 |

5

Example 93

10 3(RS)-Phenylmethoxycarbonyl-L-[5-(phenylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset S(O_2)NHC(O)(CH_2)_2$, $R^3 = \emptyset CH_2$, $R^4 = H$, $A = OCO$, $n = 1$)

15 a. 3(RS)-Phenylmethoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = HOCO(CH_2)_2$, $R^3 = \emptyset CH_2$, $R^4 = H$, $A = OCO$, $n = 1$).

Using the method of Example 14, material prepared according to the procedure of Example 90b was converted into the title product; TLC, $R_f = 0.27$, MeOH: $CHCl_3$:AcOH (2.5:95:0.1).

20 b. 3(RS)-Phenylmethoxycarbonyl-L-[5-(phenylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = \emptyset S(O_2)NHC(O)(CH_2)_2$, $R^3 = \emptyset CH_2$, $R^4 = H$, $A = OCO$, $n = 1$).

25 Using the method of Example 77b, material prepared according to the procedure of Example 93a was allowed to react with benzenesulfonamide to provide, after purification by flash chromatography (gradient, MeOH:Et₂O (2.5:97.5) to (5:95)), the title product (40%); HPLC, $t_R = 7.38$ & 10.35, Col A, H₂O:CH₃CN (65:35), FR = 2.5.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $C_{30}H_{35}F_3N_4O_8S \cdot 1.5H_2O$: | C, 51.79; | H, 5.51; | N, 8.19 |
| Found: | C, 51.70; | H, 5.24; | N, 7.89 |

30

Example 94

35 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = 4-[\emptyset S(O_2)NH-C(O)]\emptyset$, $R^4 = H$, $A = CO$, $n = 1$)

40

Using the method of Example 89, material prepared according to the procedure of Example 79 was allowed to react with benzenesulfonamide to provide, after purification by flash chromatography (EtOAc: Et₂O:AcOH (25:74.9:0.1)), the title product (33%); HPLC, $t_R = 3.71$ & 5.65, Col A, H₂O: CH₃CN (3:1); FR = 2.0.

45

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $C_{30}H_{35}F_3N_4O_7S \cdot 1.25H_2O$: | C, 53.36; | H, 5.59; | N, 8.29 |
| Found: | C, 53.75; | H, 5.64; | N, 7.72 |

50

Example 95

55 3(RS)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = 4-[(4-Br\emptyset)S(O_2)NHC(O)]\emptyset$, $R^4 = H$, $A = CO$, $n = 1$)

a. 4-Bromobenzenesulfonamide.

Using the procedure of Example 77a, 4-bromobenzenesulfonyl chloride (10.0 g, 39.6 mmol) was converted into the title product, obtained as white crystals (8.45 g, 92%); m.p 163-165°.

- 5 b. 3(RS)-[4-[(4-Bromophenyl)sulfonylamino]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4-[(4-\text{Br}-\text{C}_6\text{H}_4)\text{S}(\text{O}_2)\text{NHC}(\text{O})]\text{C}_6\text{H}_4$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

Using the method of Example 89, material prepared according to the procedure of Example 79 was allowed to react with the product of 95a to provide, after purification by recrystallization from hexane/Et₂O, the title product (50%); HPLC, $t_R = 5.25$ & 7.84 , Col A, H₂O:CH₃CN (77.5:22.5), FR = 2.0.

| | | | |
|--|-----------|----------|---------|
| Analysis calculated for: | | | |
| C ₃₀ H ₃₄ BrF ₃ N ₄ O ₇ S.0.75H ₂ O: | C, 48.36; | H, 4.80; | N, 7.52 |
| Found: | C, 48.61; | H, 4.89; | N, 7.18 |

Example 96

- 20 3(RS)-4-(1-Naphthylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 1\text{-naphthyl-S}(\text{O}_2)\text{NHC}(\text{O})(\text{CH}_2)_2$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

Using the method of Example 89 material prepared according to the procedure of Example 14 was allowed to react with 1-naphthalenesulfonamide to provide, after purification by flash chromatography (MeOH:CHCl₃ (5:95)), the title product (46%); HPLC, $t_R = 4.09$ & 6.57 , Col A, H₂O:CH₃CN (60:40), FR = 2.0.

| | | | |
|---|-----------|----------|---------|
| Analysis calculated for: | | | |
| C ₃₀ H ₃₇ F ₃ N ₄ O ₇ S.0.5H ₂ O: | C, 54.29; | H, 5.77; | N, 8.44 |
| Found: | C, 54.33; | H, 6.01; | N, 8.09 |

Example 97

- 35 3(RS)-[2-(4-Aminocarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4-[\text{H}_2\text{NC}(\text{O})]\text{C}_6\text{H}_4\text{OCH}_2$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

- 40 a. 4-Aminocarbonylphenoxyacetic acid methylester.

A mixture of p-hydroxybenzamide (3.43 g), methyl bromoacetate (2.37 ml) and K₂CO₃ (3.45 g) was stirred for 12 hr in 25 ml of DMF. The reaction mixture was diluted with water (150 ml); the solid was filtered, washed with water, and air dried. Crystallization from ethanol gave 3.3 g (63%) of the title compound as white crystals.

- b. 4-Aminocarbonylphenoxyacetic acid.

A mixture of the product of Example 97a (3.3 g) in 0.5 N NaOH (30 ml) was stirred for 3 hr. The solution was filtered and the filtrate made acidic (pH 1) with 1N HCl. The solid was filtered and air dried to yield 3.0 g (97%) of the title acid as a white powder; mp 255-256°.

- 50 c. 2(RS),3(SR)-[2-(4-aminocarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4-[\text{H}_2\text{NC}(\text{O})]\text{C}_6\text{H}_4\text{OCH}_2$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

Using the method of Example 32a, material prepared by the procedure of Example 5d was allowed to react with material prepared according to Example 97b to provide the title compound, isolated in 33% yield;

TLC, $R_f = 0.27$ & 0.31 , MeOH:CH₂Cl₂ (1:9).

d. 3(RS)-[2-(4-Aminocarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-[H}_2\text{NC(O)]}\text{OCH}_2$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 97c was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (4:96)), the title product (35%); TLC, $R_f = 0.37$, MeOH:CHCl₃ (1:9).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₅ H ₃₃ F ₃ N ₄ O ₆ ·1.5H ₂ O: | C, 52.72; | H, 6.37; | N, 9.83 |
| Found: | C, 52.78; | H, 6.03; | N, 9.65 |

Example 98

3(RS)-[4-(Hydroxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-[HOC(O)]}\text{OCH}_2$, $R^4 = \text{H}$, $A = \text{OCO}$, $n = 1$)

Using the method of Example 14, material prepared according to the procedure of Example 86c was converted into the title product and isolated by preparative TLC (MeOH:CHCl₃ (15:85)) in 45% yield; HPLC, $t_R = 2.27$ & 3.02 , Col A, H₂O:CH₃CN (60:40), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₅ H ₃₂ F ₃ N ₃ O ₇ ·2H ₂ O: | C, 51.81; | H, 6.26; | N, 7.25 |
| Found: | C, 51.75; | H, 5.63; | N, 7.15 |

Example 99

3(RS)-[4-[4-(2-Amino-2-oxoethyl)phenoxy]-1-oxobutyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-[H}_2\text{NC(O)CH}_2\text{]}\text{O}(\text{CH}_2)_3$, $R^4 = \text{H}$, $A = \text{CO}$, $n = 1$)

a. 4-(4-Aminocarbonylphenoxy)butanoic acid ethyl ester.

A mixture of p-hydroxyphenylacetamide (3.8 g), ethyl 4-bromobutyrate (3.6 ml) and K₂CO₃ (3.45 g) was stirred for 12 hr in DMF (30 ml). The mixture was diluted with water (100 ml); the solid was filtered and air dried. Crystallization of the solid from ethanol gave 4 g (60%) of the title compound as white crystals; mp 144.5-145.5°.

b. 4-(4-Aminocarbonylphenoxy)butanoic acid.

A mixture of the product of Example 99a (3.97 g) in 1N NaOH (20 ml) was stirred overnight at room temperature. The solution was filtered and made acidic with 1N HCl. The solid was filtered and dried under high vacuum to yield 3 g (82%) of the title compound as a white powder; m.p. 162.5-164°.

c. 2(RS),3(SR)-[4-[4-(2-Amino-2-oxoethyl)phenoxy]-1-oxobutyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}$, $R^3 = 4\text{-[H}_2\text{NC(O)CH}_2\text{]}\text{O}(\text{CH}_2)_3$, $R^4 = \text{H}$, $A = \text{CO}$, $N = 1$).

Using the method of Example 32a, material prepared by the procedure of Example 5d was allowed to react with the product of Example 99b to provide the title compound, isolated in 71% yield; TLC, $R_f = 0.28$ & 0.31 , MeOH:CHCl₃ (1:9).

d. 3(RS)-[4-(2-amino-2-oxoethyl)phenoxy]-1-oxobutyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-

prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4-[\text{H}_2\text{NC}(\text{O})\text{CH}_2]\text{O}(\text{CH}_2)_3$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

Using the method of Example 61c, the product of Example 99c was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (4:96)), the title product (32%); HPLC, $t_R = 2.11$ & 3.01, Col B, H₂O:CH₃CN:THF:TFA (55:35:15:0.1), FR = 2.0.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| $\text{C}_{28}\text{H}_{39}\text{F}_3\text{N}_4\text{O}_6 \cdot 5\text{H}_2\text{O}$ | C, 56.65; | H, 6.79; | N, 9.43 |
| Found: | C, 56.83; | H, 6.98; | N, 9.24 |

Example 100

3(RS)-E-[3-(4-Hydroxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = \text{E}-4-[\text{HOC}(\text{O})]\text{CH}=\text{CH}-$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

Using the method of Example 14, material prepared according to the procedure of Example 87d was converted into the title product in 88% yield; HPLC, $t_R = 2.6$ & 3.4, Col B, H₂O:CH₃CN:THF:TFA (55:35:15:0.1), FR = 1.5.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| $\text{C}_{26}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_6 \cdot 0.35\text{H}_2\text{O}$ | C, 57.21; | H, 6.03; | N, 7.96 |
| Found: | C, 57.40; | H, 6.40; | N, 7.38 |

Example 101

3(RS)-[2-(4-Ethoxycarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4-[\text{CH}_3\text{CH}_2\text{OC}(\text{O})]\text{OCH}_2$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

a. Ethyl 4-[2-Oxo-2-(phenylmethoxy)ethoxy]benzoate.

A mixture of ethyl p-hydroxybenzoate (4.98 g), benzyl bromoacetate (4.75 ml) and K₂CO₃ (4.14 g) was stirred for 15 hr in 30 ml of DMF. The reaction mixture was diluted with water (200 ml) and extracted with a 1:1 ether:hexane mixture. The combined organic extracts were washed (water, brine), dried (Na₂SO₄), filtered, and evaporated leaving 9.3 g, (99%) of the title compound as a heavy oil; TLC, $R_f = 0.71$, Et₂O:hexane (1:1).

b. Ethyl 4-(2-Hydroxy-2-oxoethoxy)benzoate.

A solution of the product of Example 101a (2.0 g) in EtOH (50 ml) was hydrogenated at 170,000 Pascals (10 psi) using 10% Pd/C (200 mg). After 20 min the reaction was complete and the reaction mixture was filtered through a pad of Celite® and concentrated under vacuum. The residue was crystallized from methyl tert-butyl ether/hexane affording 900 mg (63%) of the title compound as fine white needles; mp 129-130°.

c. 2(RS),3(SR)-[2-(4-Ethoxycarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, $R^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $R^2 = (\text{CH}_3)_2\text{CH}-$, $R^3 = 4-[\text{CH}_3\text{CH}_2\text{OC}(\text{O})]\text{OCH}_2$, $R^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$).

Using the method of Example 32a, material prepared by the procedure of Example 5d was allowed to react with the product of Example 101b to provide the title compound, isolated in 92% yield; TLC, $R_f = 0.47$

& 0.53, MeOH:CH₂Cl₂ (1:9).

- d. 3(RS)-{2-(4-Ethoxycarbonylphenoxy)-1-oxoethyl}-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[CH₃CH₂OC(O)]ØOCH₂, R⁴ = H, A = CO, n = 1).

Using the method of Example 61c, the product of Example 101c was oxidized to afford, after purification by flash chromatography (MeOH: CH₂Cl₂ (2:98)), the title product (41%); TLC, R_f = 0.37, MeOH:CHCl₃ (1:9).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₇ H ₃₆ F ₃ N ₃ O ₇ : | C, 56.74; | H, 6.35; | N, 7.35 |
| Found: | C, 56.40; | H, 6.50; | N, 7.12 |

Example 102

- 3(RS)-[3-(4-Ethoxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[CH₃CH₂OC(O)]Ø(CH₂)₂-, R⁴ = H, A = CO, n = 1)

a. 4-Ethoxycarbonylbenzenepropanoic acid.

A solution of 4-carbethoxycinnamic acid (4.9 g) in EtOH (120 ml) was hydrogenated over 5% Rh.C (485 mg) at atmospheric pressure for 21 hr. The solution was filtered and stripped. The residue was crystallized from cyclohexane to afford 2.23 g (46%) of the title compound as white crystals; mp 108.5-110.5°.

- b. 2(RS),3(SR)-[3-(4-Ethoxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[CH₃CH₂OC(O)]Ø-(CH₂)₂-, R⁴ = H, A = CO, n = 1).

Using the method of Example 32a, material prepared by the procedure of Example 5d was allowed to react with the product of Example 102a to produce the title compound, isolated in 83% yield after purification by flash chromatography (MeOH:CH₂Cl₂ (4:96)); TLC, R_f = 0.33 & 0.38, MeOH:CH₂Cl₂ (5:95).

- c. 3(RS)-[3-(4-Ethoxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[CH₃CH₂OC(O)]Ø(CH₂)₂-, R⁴ = H, A = CO, n = 1).

Using the method of Example 84d, the product of Example 102b was oxidized to afford the title product (97%).

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₈ H ₃₈ F ₃ N ₃ O ₆ * 0.65 H ₂ O: | C, 57.85; | H, 6.81; | N, 7.23 |
| Found: | C, 57.89; | H, 6.83; | N, 6.98 |

Example 103

3(RS)-4-Hydroxybenzoyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-(HO)Ø, R⁴ = H, A = CO, n = 1)

- a. 2(RS),3(SR)-4-Hydroxybenzoyl-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-(HO)Ø, R⁴ = H, A = CO, n = 1).

Using the method of Example 84b, material prepared by the procedure of Example 5d was allowed to react with 4-hydroxybenzoic acid to provide the title compound which was isolated in 65% yield after purification by flash chromatography (EtOAc:Et₂O (15:85)); TLC, R_f = 0.43, EtOAc:Et₂O (15:85).

5

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₃ H ₃₂ F ₃ N ₃ O ₅ ·0.6H ₂ O: | C, 55.43; | H, 6.71; | N, 8.43 |
| Found: | C, 55.76; | H, 6.62; | N, 8.03 |

10

b. 3(RS)-4-Hydroxybenzoyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-(HO)Ø, R⁴ = H, A = CO, n = 1).

15

The product of Example 103a was oxidized by the method of Example 33c with the following, modified workup: The crude residue was dissolved in MeOH and stirred with aq K₂CO₃ (5 ml) at room temperature for 16 hr. After the mixture was partially concentrated under vacuum, it was acidified with conc HCl and extracted with EtOAc. The EtOAc solution was washed (brine), dried (Na₂SO₄), filtered, and concentrated to a residue which was purified by flash chromatography (EtOAc:Et₂O (1:9)) to afford the title compound in 38% yield; HPLC, t_R = 3.54 & 4.92, Col A, CH₃CN:H₂O (35:65), FR = 2.0.

20

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₃ H ₃₀ F ₃ N ₃ O ₅ ·1.2 H ₂ O: | C, 54.47; | H, 6.44; | N, 6.29 |
| Found: | C, 54.83; | H, 6.49; | N, 7.89 |

25

Example 104

30

3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[(4-ClØ)S(O₂)NHC(O)]Ø-, R⁴ = H, A = CO, n = 1)

35

Using the method of Example 77b, material prepared according to the procedure of Example 79 was allowed to react with 4-chlorobenzenesulfonamide to provide, after purification by flash chromatography (MeOH:CH₂Cl₂ (3:97)) and acidification of the chromatographed product with MeOH and 1N HCl as described in Example 121d, the title product (66%), HPLC, t_R = 4.26 & 6.07, Col A, H₂O:CH₃CN:THF:TFA (55:35:15:0.1).

40

Example 105

3(RS)-[3-(4-Hydroxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[HOC(O)]Ø(CH₂)₂, R⁴ = H, A = CO, n = 1)

45

Using the method of Example 14, material prepared according to the procedure of Example 102c was converted into the title product in 81% yield; HPLC, t_R = 2.6 & 3.4, Col B, H₂O:CH₃CN:THF:TFA (55:35:15:0.1).

50

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₆ H ₃₄ F ₃ N ₃ O ₆ : | C, 57.66; | H, 6.33; | N, 7.76 |
| Found: | C, 56.98; | H, 6.49; | N, 7.35 |

55

Example 106

3(RS)-[3-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[(4-ClØ)S(O₂)-

$\text{NHC(O)}\text{O}-(\text{CH}_2)_2$, $\text{R}^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

Using the method of Example 77b, material prepared according to the procedure of Example 105 was allowed to react with 4-chlorobenzenesulfonamide to provide, after purification by flash chromatography (MeOH:CH₂Cl₂ (5:95)), the title product (90%); HPLC, $t_R = 3.96$ & 5.73 , Col B, H₂O:CH₃CN:THF:TFA (55:35:15: 0.1), FR = 3.0.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| C ₃₂ H ₃₈ ClF ₃ N ₄ O ₇ S.1.7 H ₂ O: | C, 51.53; | H, 5.59; | N, 7.51 |
| Found: | C, 51.72; | H, 5.40; | N, 7.24 |

Example 107

3(RS)-E-[3-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = (\text{CH}_3)_2\text{CH}-$, $\text{R}^3 = \text{E}-[4-[(4-\text{Cl})\text{S}-(\text{O}_2)\text{NHC(O)}\text{O}]\text{CH}=\text{CH}-$, $\text{R}^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

Using the method of Example 77b, material prepared according to the procedure of Example 100 was allowed to react with 4-chlorobenzenesulfonamide to provide, after purification by flash chromatography (MeOH:CH₂Cl₂ (5:95)), the title product (97%); HPLC, $t_R = 4.73$ & 6.68 , Col B, H₂O:CH₃CN:THF:TFA (55:35:15: 0.1), FR = 3.0.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| C ₃₂ H ₃₅ ClF ₃ N ₄ O ₇ S.1.7 H ₂ O: | C, 51.67; | H, 5.33; | N, 7.53 |
| Found: | C, 51.72; | H, 5.40; | N, 7.24 |

Example 108

3(RS)-[1-[4-[(4-Bromophenyl)sulfonyl][phenylmethyl]aminocarbonyl]phenyl]-1-oxomethyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $\text{R}^1 = \text{CH}(\text{CH}_3)\text{CH}_3$, $\text{R}^2 = (\text{CH}_3)_2\text{CH}-$, $\text{R}^3 = 4-[(4-\text{Br})\text{S}(\text{O}_2)\text{N}(\text{CH}_2\text{O})\text{C(O)}]\text{O}-$, $\text{R}^4 = \text{H}$, $\text{A} = \text{CO}$, $n = 1$)

a. 4-Bromo-N-(phenylmethyl)benzenesulfonamide.

4-Bromobenzenesulfonyl chloride (14.05 g, 55 mmol) was added to a stirred solution of benzylamine (5.36 g, 50 mmol) and pyridine (400 ml) under nitrogen at room temperature. The resulting reaction mixture was stirred for 1 hr; then it was poured onto ice/water (800 ml) to form a yellow precipitate which was filtered and recrystallized from EtOH/water to give 9.44 g (53%) of the title compound as off-white needles, mp 116-117°C.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| C ₁₃ H ₁₂ BrNO ₂ S: | C, 47.87; | H, 3.71; | N, 4.29 |
| Found: | C, 48.02; | H, 3.78; | N, 4.25 |

b. 1,1-Dimethylethyl 4-[(4-bromophenyl)sulfonyl][phenylmethyl]aminocarbonyl]benzoate.

DMAP (1.81 g, 14.84 mmol) was added to a stirred solution of the product of Example 108a (4.4 g, 13.49 mmol) and CH₂Cl₂ (150 ml) at room temperature. To the resulting solution, WSCDI (2.84 g, 14.84 mmol) and terephthalic acid mono t-butylester (3.0 g, 13.49 mmol) were successively added. The reaction mixture was stirred at room temperature overnight and concentrated under vacuum to leave a residue which was dissolved in EtOAc. The EtOAc solution was washed (20% aq citric acid solution, brine, water), dried

(MgSO₄), filtered, and concentrated under vacuum to leave an oily residue. This residue was dissolved in warm EtOH and allowed to cool. The white crystals which formed were filtered, washed with cold EtOH, and dried under high vacuum to give 5.72 g (80%) of the title compound as white crystals; m.p. 120-122 °C.

5

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₅ H ₂₄ BrNO ₅ S: | C, 56.61; | H, 4.56; | N, 2.64 |
| Found: | C, 56.84; | H, 4.68; | N, 2.60 |

10

c. 4-[[[4-Bromophenyl)sulfonyl][phenylmethyl]aminocarbonyl]benzoic acid.

The product of Example 108b (5.30 g, 10 mmol) was added to TFA (50 ml) at 0 ° and dissolved immediately upon addition. After about 10 min a white precipitate formed; stirring was continued for ½ hr before the mixture was filtered. The collected solid was washed with water and recrystallized from hot absolute EtOH to give 4.0 g (84%) of the title compound as a white powder; m.p. 193-194 °C.

d. 2(RS),3(RS)[1-[4-[[[4-Bromophenyl)sulfonyl][phenylmethyl]aminocarbonyl]phenyl]-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = 4-[[[4-BrO)S(O₂)]-(OCH₂)NCO]Ø, R⁴ = H, A = CO, n = 1).

WSCDI (0.44 g, 2.3 mmol) was added to a stirred solution of the product of Example 108c (1.0 g, 2.1 mmol), material prepared according to Example 5d (0.85 g, 2.3 mmol), HOBT (0.28 g, 2.1 mmol) and dry THF under nitrogen at 0 °. The resulting reaction mixture was stirred at 0 °C for 15 min; then it was allowed to warm to room temperature and stirred for 4 hr. The THF was removed under vacuum to leave a brownish residue which was dissolved in EtOAc. The EtOAc solution was washed (1N HCl, satd NaHCO₃, brine) and dried (MgSO₄), filtered, and concentrated under vacuum to leave a residue (1.6 g). A (1.27 g) portion of this residue was recrystallized from methyl t-butyl ether/hexane to give 0.64 g (49% overall yield) of the title compound as a white powder; TLC, R_f = 0.59 & 0.64, CHCl₃:CH₃OH (95:5); HPLC; t_R = 14.34 & 15.26, Col B, H₂O:CH₃CN:THF:TFA (55:35:15:0.1), FR = 3.0.

e. 3(RS)-[1-[4-[[[4-Bromophenyl)sulfonyl][phenylmethyl]aminocarbonyl]phenyl]-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[[[4-BrO)S(O₂)]N(CH₂Ø)C(O)Ø, R⁴ = H, A = CO, n = 1).

A solution of the product of Example 108d (300 mg, 0.364 mmol) in CH₂Cl₂ (2 ml) was added to a stirred mixture of a Dess-Martin periodinane (1.54 g, 3.63 mmol) and dry CH₂Cl₂ (10 ml) under nitrogen at room temperature. To the resulting mixture, TFA (0.41 g, 3.63 mmol) was added; whereupon the mixture immediately became clear; then, after 10 min, became cloudy. Stirring was continued overnight before EtOAc (50 ml) was added, and the resulting mixture was poured into saturated aq NaHCO₃ (100 ml) containing 4 g of Na₂S₂O₃. The two phase mixture was stirred vigorously for 10 min. The organic layer was separated, washed (satd NaHCO₃ (100 ml), brine (100 ml)), dried (MgSO₄), filtered, concentrated under vacuum, and dried under high vacuum to give 0.24 g (80%) of the title compound as a white powder; TLC, R_f = 0.62 & 0.75, CHCl₃:MeOH (95:5); HPLC, t_R = 14.88 & 21.56, Col B, H₂O: CH₃CN:THF:TFA (55:35:15:0.1), FR = 3.0.

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| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₃₇ H ₄₀ BrF ₃ N ₄ O ₇ S.O.25H ₂ O: | C, 53.78; | H, 4.94; | N, 6.78 |
| Found: | C, 53.84; | H, 4.98; | N, 6.45 |

Example 109

55

3R(orS)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 1-adamantyl, R⁴ = H, A = S(O₂), n = 1)

From the flash chromatography described in Example 91c was obtained the title compound as the other substantially pure isomer (84%); HPLC, t_R = 3.89, Col A, H₂O:CH₃CN (45:55), FR = 2.0.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₆ H ₄₀ F ₃ N ₃ O ₅ S.0.5H ₂ O: | C, 54.57; | H, 7.22; | N, 7.34 |
| Found: | C, 54.52; | H, 7.15; | N, 7.33 |

Example 110

3S(orR)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[ØS(O₂)NHC(O)]Ø, R⁴ = H, A = NHCO, n = 1)

The two diastereomers of Example 58 were separated by MPLC on a LiChroprep® RP-8 column (Merck, Size B 40-63 µm) using MeOH:H₂O (50:50) as eluent. The fractions collected were analyzed by HPLC, and the appropriate fractions were combined and lyophilized to give the title product; HPLC, t_R = 4.5, Col B, H₂O: CH₃CN:THF:TFA (55:35:15:0.1), FR = 2.0.

Example 111

3S(or R)-Phenylmethoxycarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = Ø, R³ = ØCH₂-, R⁴ = H, A = OCO, n = 1)

Using the method of Example 61c, the product prepared by the method of Example 92a was oxidized to afford, after purification by flash chromatography (MeOH:CH₂Cl₂ (1.5:98.5)), the title product (80%) as one substantially pure isomer; TLC, R_f = 0.26, pentane: MeOH:Et₂O (25:1:99).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₇ H ₃₀ F ₃ N ₃ O ₅ : | C, 60.78; | H, 5.67; | N, 7.88 |
| Found: | C, 60.64; | H, 5.85; | N, 7.96 |

Example 112

3R(orS)-Phenylmethoxycarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = Ø, R³ = ØCH₂-, R⁴ = H, A = OCO, n = 1)

From the flash chromatography described in Example 111 was obtained the title product (83%) as the other substantially pure isomer; TLC, R_f = 0.30, pentane:MeOH:Et₂O (25:1:99).

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₇ H ₃₀ F ₃ N ₃ O ₅ : | C, 60.78; | H, 5.67; | N, 7.88 |
| Found: | C, 59.43; | H, 5.65; | N, 7.48 |

Example 113

3R(orS)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-pentyl)]-L-prolinamide (Formula Ib, R¹ = CH(CH₃)CH₃, R² = (CH₃)₂CH-, R³ = 4-[4-(BrØ)S(O₂)NHC(O)]Ø, R⁴ = H, A = CO, n = 1)

The product of Example 95b (0.5 g, 0.7 mmol) was chromatographed by MPLC on a LiChroprep® RP-8 column (Merck, size B 40-63 µm) using MeOH:H₂O (60:40) as eluent. The fractions collected were

evaluated by HPLC, combined, and lyophilized to give two products. The title product (0.147 g) was obtained as a substantially pure isomer; HPLC, t_R = 12.38, Col B, $H_2O:CH_3CN:THF:TFA$ (55:35:15:0.1), FR = 3.0.

5 Example 114

3S(or R)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = 4-[(4-Br\phi)S(O_2)NHC(O)]\phi$, $R^4 = H$, $A = CO$, $n = 1$)

The other product obtained in the separation described in Example 113 was the title product (0.065 g), obtained as a substantially pure isomer; HPLC, t_R = 8.44, Col B, $H_2O:CH_3CN:THF:TFA$ (55:35:15:0.1), FR = 3.0.

15 Example 115

3S(or R)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = 4-[(4-Cl\phi)S(O_2)NHC(O)]\phi$, $R^4 = H$, $A = CO$, $n = 1$)

A portion of material prepared as described in Example 104 (544.8 mg) was dissolved in $H_2O:CH_3CN:THF$ (2.2 ml:3.3 ml:0.5 ml) and was separated by MPLC on a Lobar® size B LiChroprep® RP-8 column using $H_2O:CH_3CN:THF:TFA$ (55:32.5:12.5:0.1). After analysis by HPLC, the appropriate fractions were combined, concentrated under vacuum, and dried under high vacuum at 43° to afford the title compound (255 mg) as a white amorphous solid; HPLC, t_R = 5.76, Col B, $H_2O:CH_3CN:THF:TFA$ (55:32.5:12.5:0.1), FR = 3.0.

Analysis calculated for:

| | | | |
|--|-----------|----------|---------|
| $C_{30}H_{34}ClF_3N_4O_7S \cdot 1.3H_2O$ | C, 50.71; | H, 5.19; | N, 7.89 |
| Found: | C, 50.88; | H, 4.87; | N, 7.70 |

35 Example 116

3R(or S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = (CH_3)_2CH-$, $R^3 = 4-[(4-Cl\phi)S(O_2)NHC(O)]\phi$, $R^4 = H$, $A = CO$, $n = 1$)

A portion of material prepared as described in Example 104 (573.8 mg) was dissolved in $H_2O:THF$ (2 ml:3 ml) and was separated by MPLC on a Lobar® size B LiChroprep® RP-8 column using $THF:H_2O:TFA$ (41:59:0.1) as eluent. After analysis by HPLC, the appropriate fractions were combined and lyophilized to afford the title compound (51.8 mg) as a substantially pure isomer (99:1 by HPLC); HPLC, t_R = 8.8, Col B, $H_2O:CH_3CN:THF:TFA$ (55:32.5:12.5:0.1), FR = 3.0.

Example 117

3S(or R)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, $R^1 = CH(CH_3)CH_3$, $R^2 = CH(CH_3)CH_3$, $R^3 = \phi CH_2$, $R^4 = H$, $A = OCO$, $n = 1$)

A portion of material prepared according to the method of Example 11 (10 g, 0.92 mol) was separated into its individual substantially optically pure isomers by flash chromatography (1 kg of silica gel, Et_2O :hexane (80:20)). Combination of the appropriate fractions afforded the title compound (3.17 g) as a substantially pure isomer; HPLC, t_R = 5.65, Col A, $H_2O:CH_3CN$ (55:45), FR = 2.0.

| Analysis calculated for: | | | |
|---|-----------|----------|---------|
| C ₂₄ H ₃₂ F ₃ N ₃ O ₅ ·H ₂ O: | C, 55.47; | H, 6.46; | N, 8.08 |
| Found: | C, 55.50; | H, 6.77; | N, 7.99 |

Example 118

3R(or S)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula 1b, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = ∅CH₂, R⁴ = H, A = OCO, n = 1)

From the separation described in Example 117 combination of the appropriate fractions afforded the title compound (3.67 g) as the other substantially pure isomer.

| Analysis calculated for: | | | |
|--|-----------|----------|---------|
| C ₂₄ H ₃₂ F ₃ N ₃ O ₅ : | C, 57.71; | H, 6.46; | N, 8.41 |
| Found: | C, 57.61; | H, 6.34; | N, 7.96 |

Example 119

32(or R)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula 1b, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = 4-(HOOC)∅, R⁴ = H, A = NHCO, n = 1)

A portion of a product prepared as described in Example 16 (500 mg) was separated by MPLC on a Lobar® size B LiChroprep® RP-8 column using MeOH:H₂O (1:1) as eluent. After analysis by HPLC, the appropriate fractions were combined to afford the title compound (150 mg) as a substantially pure isomer; HPLC, t_R = 6.58, Col A, CH₃CN:H₂O (25:75), FR = 2.0.

Example 120

3R(or S)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula 1b, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = 4-(HOOC)∅, R⁴ = H, A = NHCO, n = 1)

By combination of the appropriate fractions from the separation described in Example 119, the title compound was obtained as a highly enriched isomer (220 mg) in a ratio of 90.4:9.5 with the isomer described in Example 119; HPLC, t_R = 11.09, Col A, CH₃CN:H₂O (25:75), FR = 2.0.

Example 121

3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula 1b, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = 4-[(4-Cl∅)S(O₂)NHCO]∅, R⁴ = H, A = CO, n = 1)

A preferred method for conversion of material prepared using the method of Example 5d into the title compound is as follows:

a. 1,1-Dimethylethyl 4-[(4-chlorophenyl)sulfonylaminocarbonyl]benzoate.

A 5-liter 3-neck round bottom flask was equipped with a mechanical stirrer and nitrogen inlet. CH₂Cl₂ (2 liters) was placed in the reaction flask and terephthalic acid mono-t-butyl ester (127.5 g, 0.574 mol), DMAP (70.06 g, 0.574 mol), and 4-chlorobenzenesulfonamide (110.04 g, 0.574 mol) were added in that order using CH₂Cl₂ (400 ml) to wash down the solids. WSCI (110.10 g, 0.574 mol) was added in portions over 10 min using CH₂Cl₂ (100 ml) to wash down the solid. After the reaction mixture was stirred overnight at room temperature, it was concentrated under vacuum to dryness. The residue was partitioned between EtOAc and water. The EtOAc solution was washed (20% aq citric acid, satd aq NaHCO₃, brine), dried (Na₂SO₄), and

concentrated under vacuum to a white solid. After drying in a vacuum oven at 50°, the title product (227 g, 100%) was obtained in a sufficiently pure state to be used directly for the next step; TLC, R_f = 0.43, MeOH:CHCl₃ (15:85). (Further purification was possible by recrystallization from EtOH:water; m.p. above 300°).

b. 4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzenecarboxylic acid.

A 3-liter 3-neck round bottom flask was equipped with a mechanical stirrer and a CaCl₂ drying tube. TFA (1300 g) was added and cooled to 0°; and the product of Example 121a (79.5 g, 0.20 mol) was added. Initially, the solid dissolved, giving a clear solution. After 10-15 min, a heavy precipitate of product formed, and it was difficult to stir the reaction mixture. Vigorous stirring with the mechanical stirrer was essential to drive the reaction to completion. The reaction mixture was stirred at 0-5° for 1 hr before it was poured onto 1500 ml of ice/water and stirred for 2 hr. The resulting solid was filtered and dried. The white solid (61.5 g, 91%) obtained was recrystallized from 1600 ml absolute EtOH/1600 ml H₂O to yield the title product (54 g, 80%) as white needles; m.p. = 286-288°; TLC, R_f = 0.7, MeOH:CHCl₃: AcOH (10:90:1).

c. 2(RS),3(SR)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R^1 = CH(CH₃)CH₃, R^2 = CH(CH₃)CH₃, R^3 = 4-[(4-Cl-Ø)-S(O₂)NHCO]Ø, R^4 = H, A = CO, n = 1).

A 250 ml 3-neck round bottom flask was equipped with a magnetic stirrer and nitrogen inlet. To CH₂Cl₂ (125 ml) in the reaction flask, the product of Example 121b (5.45 g, 16.07 mmol), DMAP (1.96 g, 16.07 mmol), and material prepared according to Example 5d (6.20 g, 16.87 mmol) were added using CH₂Cl₂ (20 ml) to wash down the solids; then, WSCDI (3.24 g, 16.87 mmol) was added using CH₂Cl₂ (5 ml) to wash down the solid. After the reaction mixture had been stirred for 5 hr, it was washed (1N HCl, satd aq NaHCO₃, brine), dried (Na₂SO₄), and concentrated under vacuum to afford a crude product (11.0 g, 100%) as a white solid. A portion (3.39 g) of this crude product was dissolved in MeOH (40 ml) and diluted with water (9 ml). The resulting solution was saturated with K₂CO₃ and stirred overnight at room temperature. After most of the MeOH had been removed under vacuum, the residue was partitioned between EtOAc and water. The EtOAc solution was washed (satd aq NaHCO₃, brine), dried (Na₂SO₄), and concentrated to afford a substantially pure title product (3.13 g, 92%); TLC, R_f = 0.38 & 0.46, MeOH:CHCl₃:AcOH (5:95:1); HPLC, t_R = 6.20 & 6.25, Col A, H₂O:CH₃CN:THF:TFA (55:35:15:0.1), FR = 3.0.

d. 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R^1 = CH(CH₃)CH₃, R^2 = CH(CH₃)CH₃, R^3 = 4-[(4-ClØ)S(O₂)-NHCO]Ø, R^4 = H, A = CO, n = 1).

To a stirred solution of Dess-Martin periodinane (636 g, 1.50 mol) in CH₂Cl₂ (5 liter) was added product prepared using the method of Example 121c (351 g, 0.50 mol) in THF (500 ml), and the resulting suspension was diluted with CH₂Cl₂ (2 liter), followed by the addition of TFA (171 g, 1.50 mol). After the reaction mixture had been stirred overnight at room temperature, the CH₂Cl₂ was removed under vacuum, the residue was diluted with EtOAc and treated with a 1:1 mixture of said aq NaHCO₃ and satd aq Na₂S₂O₃. When all the solid had dissolved, the aq layer was separated and the EtOAc layer was washed (a mixture of satd aq NaHCO₃:satd aq Na₂SO₃ (1:1), satd aq NaHCO₃, brine), dried (Na₂SO₄) and concentrated under vacuum. The residue was dissolved in MeOH (1.5 liter) and treated with 1N HCl (1.5 liter), and the MeOH was removed under vacuum. The aq suspension remaining was extracted with CH₂Cl₂, and the combined CH₂Cl₂ extracts washed (brine) dried (Na₂SO₄), and concentrated under vacuum to afford after purification by flash chromatography (gradient, Et₂O to Et₂O:MeOH (95:5)) and acidification of the chromatographed product with MeOH 1N HCl as described above, the title product (37%); HPLC, t_R = 6.68 & 9.27, Col B, H₂O:CH₃CN:THF:TFA (55:35:15:0.1), FR = 2.0.

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₃₀ H ₃₄ ClF ₃ N ₄ O ₇ S: | C, 52.44; | H, 4.99; | N, 8.15 |
| Found: | C, 52.31; | H, 5.20; | N, 8.20 |

Example 122

3(RS)-N²,N⁶-Di(phenylmethoxycarbonyl)-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ic, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = ØCH₂, R⁴ = H, R⁵ = ØCH₂OCONH(CH₂)₄, R⁶ = H, A = OCO, n = 1)

5 Using the method of Example 54b, the product of Example 28a was oxidized to afford, after purification by flash chromatography (hexane:Et₂O (1:1), then Et₂O, then Et₂O:EtOAc (3:1)), the title product (56%); HPLC, t_R = 4.19 & 6.02, Col A, CH₃CN:H₂O (60:40), FR = 1.5.

| | | | |
|--|-----------|----------|---------|
| Analysis calculated for: | | | |
| C ₃₈ H ₅₀ F ₃ N ₅ O ₈ .0.5H ₂ O: | C, 59.21; | H, 6.67; | N, 9.03 |
| Found: | C, 58.93; | H, 6.62; | N, 8.75 |

15 Example 123

3(RS)-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-L-norleucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ic, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = ØS(O₂)NHCO(CH₂)₂, R⁴ = H, R⁵ = (CH₂)₃CH₃, R⁶ = H, A = CO, n = 1)

20 A solution of the product of Example 24 (0.5 g, 0.87 mmol), benzenesulfonamide (0.14 g, 0.87 mmol), DMAP (0.11 g, 0.87 mmol) and DCC (0.18 g, 0.87 mmol) in CH₂Cl₂ (20 ml) was stirred for four days at room temperature. The reaction mixture was filtered and concentrated under vacuum to give a crude product. The product was purified by flash chromatography on Baker pH 5.0 silica gel (gradient, CHCl₃ to MeOH:CHCl₃ (2:98) to MeOH:CHCl₃ (5:95)) to give the title product (0.37 g); HPLC, t_R = 3.84 & 5.03, Col A, H₂O:CH₃CN (65:35), FR = 1.0.

| | | | |
|---|-----------|----------|---------|
| Analysis calculated for: | | | |
| C ₃₂ H ₄₆ F ₃ N ₅ O ₈ S: | C, 52.23; | H, 6.57; | N, 9.52 |
| Found: | C, 51.94; | H, 6.29; | N, 9.37 |

35 Example 124

3(RS)-[4-(Methylsulfonylamino)-1,4-dioxobutyl]-L-norleucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ic, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = CH₃S(O₂)NHCO(CH₂)₂, R⁴ = H, R⁵ = (CH₂)₃CH₃, R⁶ = H, A = CO, n = 1)

40 A solution of the product of Example 24 (0.5 g, 0.87 mmol), methanesulfonamide (0.082 g, 0.87 mmol), DMAP (0.11 g, 0.87 mmol) and DCC (0.18 g, 0.87 mmol) in CH₂Cl₂ (20 ml) was stirred for four days at room temperature. The reaction was filtered and concentrated under vacuum to give a crude product which was partially purified by flash chromatography on Baker pH 5.5 silica gel (gradient, CHCl₃, MeOH:CHCl₃ - (1:99) to (2.5:97.5)). The partially purified product was partitioned between EtOAc and a mixture of aqueous 1N HCl and brine. The organic phase was dried (Na₂SO₄), filtered, and concentrated to give the title product (0.28 g); HPLC, t_R = 5.99 & 8.95, Col A, H₂O: CH₃CN (65:35), FR = 1.0.

| | | | |
|---|-----------|----------|----------|
| Analysis calculated for: | | | |
| C ₂₇ H ₄₄ F ₃ N ₅ O ₈ S: | C, 49.46; | H, 6.76; | N, 10.68 |
| Found: | C, 49.07; | H, 6.79; | N, 10.43 |

55 Example 125

3(RS)-N²-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-N⁶-phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ic, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = ØS-

(O₂)NHCO(CH₂)₂, R⁴ = H, R⁵ = ØCH₂OCONH(CH₂)₄, R⁶ = H, A = CO, n = 1)

A solution of the product of Example 27 (493 mg, 0.670 mmol), benzenesulfonamide (117 mg, 0.745 mmol), DMAP (91 mg, 0.745 mmol), and DCC (153 mg, 0.745 mmol) in CH₂Cl₂ (20 ml) was stirred at room temperature for 24 hr. The solution was diluted with EtOAc, washed (water), dried (MgSO₄), filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on Baker pH 5.5 silica gel (CH₃OH:CHCl₃ (2.5:97.5)) to afford the title product (243 mg) as a white powder; TLC, R_f = 0.50, CH₃OH:CHCl₃:AcOH (5:94:1).

Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₄₀ H ₅₃ F ₃ N ₆ O ₁₀ S.0.75H ₂ O: | C, 54.56; | H, 6.24; | N, 9.54 |
| Found: | C, 54.52; | H, 6.23; | N, 9.48 |

Example 126

3(RS)-[1,4-Dioxo-4-[(tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonylamino]butyl]-L-norleucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ic, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = (1-adamantyl)S-(O₂)NHCO(CH₂)₂, R⁴ = H, R⁵ = (CH₂)₃CH₃, R⁶ = H, A = CO, n = 1)

a. 1-Adamantanesulfinamide.

To the product of Example 82a (10.0g, 45.7 mmol) was slowly added conc ammonium hydroxide (300 ml) and the mixture was heated to reflux for three hr. After distillation of the ammonium hydroxide, the residue was taken up in water and extracted with Et₂O. The Et₂O layer was washed (brine), dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude product was purified by suction chromatography on silica gel (Et₂O to EtOAc) to give the product (4.2g) as a white solid; m.p. 139-141 ° (Lit. 141-142 °).

b. 1-Adamantanesulfonamide.

To a solution of the product of Example 126a (4.0 g, 20.0 mmol) in acetone (150 ml) at reflux was added a satd acetone solution of KMnO₄ until a faint violet color persisted. The solution was cooled, filtered through Celite® and concentrated under vacuum to give the product (3.2g) as a solid; m.p. = 191-193 ° (Lit. 197-198 °); TLC, R_f = 0.80, EtOAc.

c. 3(RS)-[1,4-Dioxo-4-[(tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonylamino]butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ic, R¹ = CH(CH₃)CH₃, R² = CH(CH₃)CH₃, R³ = (1-adamantyl)S-(O₂)NHCO(CH₂)₂, R⁴ = H, R⁵ = (CH₂)₃CH₃, R⁶ = H, A = CO, n = 1).

A solution of the product of Example 24 (300 mg, 0.51 mmol), DMAP (62 mg, 0.51 mmol), WSCDI (99 mg, 0.51 mmol) and the product of Example 126b (110 mg, 0.51 mmol) in CH₂Cl₂ (30 ml) was stirred at room temperature for 16 hr. The CH₂Cl₂ solution was washed (1N HCl, brine), dried (MgSO₄), filtered, and concentrated under vacuum. The crude product was purified by preparative TLC (MeOH:CHCl₃ (1:9)) to give the title product as a solid; TLC, R_f = 0.56, MeOH:CHCl₃ (5:95); HPLC, t_R = 4.23 & 7.05, Col A, H₂O:CH₃CN (1:1), FR = 2.0.

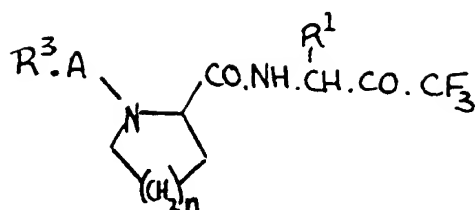
Analysis calculated for:

| | | | |
|---|-----------|----------|---------|
| C ₃₆ H ₅₆ F ₃ N ₅ O ₈ S.1.2H ₂ O: | C, 54.22; | H, 7.38; | N, 7.78 |
| Found: | C, 54.28; | H, 7.84; | N, 7.71 |

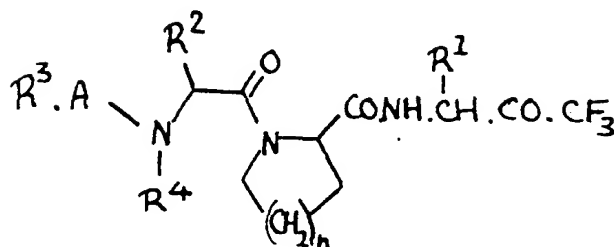
Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

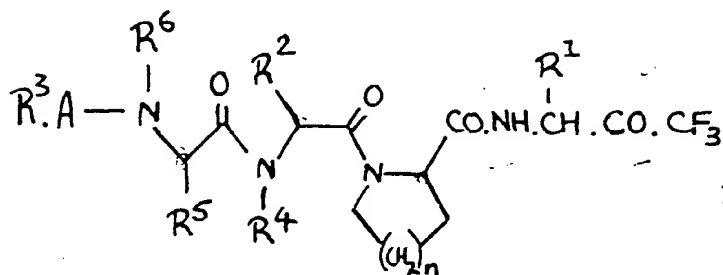
1. A compound of formula Ia, Ib or Ic:



Ia



Ib



Ic

wherein

R¹ is an alkyl group containing from 1 to 5 carbon atoms, and more preferably from 2 to 5 carbons;

R² and R⁵ are each selected independently from the group consisting of:

(I) an alkyl group containing from 1 to 10 carbons;

(II) an alkyl group containing from 1 to 6 carbon atoms substituted by at least one member selected from the group consisting of:

(a) hydroxy;

(b) amino;

(c) alkylamino containing from 1 to 6 carbons;

(d) dialkylamino wherein each alkyl group contains from 1 to 6 carbons;

(e) alkanoyl containing from 1 to 6 carbons;

(f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;

(g) aralkanoyl containing 8 to 13 carbons;

(h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;

(i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;

(j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;

(k) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons;

(l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;

(m) arylaminocarbonyl wherein the aryl group contains 6, 10 or 12 carbons;

(n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;

(o) carboxy;

(p) aryloxy carbonyl wherein the aryl group contains 6, 10 or 12 carbons;

(q) aralkoxy carbonyl wherein the aralkoxy group contains from 7 to 13 carbons;

(r) alkanoyloxy containing from 1 to 6 carbons;

(s) aryloxy wherein the aryl portion contains 6, 10 or 12 carbons;

(t) aralkanoyloxy containing from 8 to 14 carbons;

(u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;

- (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;
 (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons;
 (x) acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
 (y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 6 carbons;
 (z) aralkoxycarbonylamino wherein the aralkoxy group contains from 8 to 13 carbons (e.g., benzyloxycarbonyl amino);
 (aa) aryloxycarbonylamino wherein the aryloxy group contains 6, 10 or 12 carbons;
 (bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 6 carbons;
 (cc) aryl containing 6, 10 or 12 carbons (e.g., phenyl, biphenyl, naphthyl);
 (dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members selected from the group consisting of chloro, bromo, iodo, fluoro, trifluoromethyl, hydroxy, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
 (ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl).
 (ff) alkylureido wherein the alkyl group contains from 1 to 6 carbons;
 (gg) aralkylureido wherein the aralkyl group contains from 8 to 13 carbons;
 (hh) arylureido wherein the aryl group contains 6, 10 or 12 carbons; and
 (III) an aryl group of 6 carbons, e.g. phenyl.
- R³ is selected from the group consisting of:
- (I) an alkyl group containing from 1 to 12 carbons;
 (II) an alkyl group containing from 1 to 12 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen;
 (III) an alkyl group containing from 1 to 12 carbons and, optionally, 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, and substituted on at least one of carbon or nitrogen by 1 to 3 members selected independently from the group consisting of:
- For carbon:
- (a) hydroxy, provided that it may not be on a carbon directly bonded to A;
 (b) amino, provided that it may not be on a carbon directly bonded to A;
 (c) alkylamino containing from 1 to 6 carbons, provided that it may not be on a carbon directly bonded to A;
 (d) dialkylamino wherein each alkyl group contains from 1 to 6 carbons, provided that it may not be on a carbon directly bonded to A;
 (e) alkanoyl containing from 1 to 6 carbons;
 (f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;
 (g) aralkanoyl containing 8 to 13 carbons;
 (h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;
 (i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;
 (j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;
 (k) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons;
 (k)-(1) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
 (l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;
 (l)-(1) aralkylcarbonylamino wherein the aralkyl group contains 7 to 13 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
 (m) arylaminocarbonyl wherein the aryl group contains 6, 10 or 12 carbons;
 (n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;

- (o) carboxy;
- (p) aryloxy carbonyl wherein the aryl group contains 6, 10 or 12 carbons;
- (q) aralkoxycarbonyl wherein the aralkoxy group contains from 7 to 13 carbons;
- (r) alkanoyloxy containing from 1 to 6 carbons;
- (s) aroyloxy wherein the aryl portion contains 6, 10 or 12 carbons;
- (t) aralkanoyloxy containing from 8 to 13 carbons;
- (u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;
- (u)-(1) cycloalkylsulfonamido wherein the cycloalkyl portion contains 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);
- (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;
- (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons;
- (x) acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide, and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 6 carbons;
- (z) aralkoxycarbonylamino wherein the aralkoxy group contains from 8 to 13 carbons (e.g., benzyloxy carbonylamino);
- (z)-(1) aralkylaminocarbonyloxy wherein the aralkyl group contains 8 to 13 carbons;
- (z)-(2) aryloxy wherein the aryl contains 6, 10 or 12 carbons;
- (z)-(3) aryloxy wherein the aryl contains 6, 10 or 12 carbons and is substituted by a member selected from aminocarbonyl, aminocarbonylalkyl where the alkyl has 1 to 3 carbons, alkoxycarbonyl having 1 to 3 carbons, and carboxy;
- (aa) aryloxy carbonylamino wherein the aryloxy group contains 6, 10 or 12 carbons;
- (aa)-(1) arylaminocarbonyloxy wherein the aryl group contains 6, 10 or 12 carbons;
- (bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 6 carbons;
- (bb)-(1) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons and is optionally bonded on carbon to a carbon of an aromatic heterocyclic group as described in (gg) under R³;
- (bb)-(2) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons substituted by an aliphatic heterocyclic group as described in (ff) under R³;
- (bb)-(3) aryloxyalkyl carbonylamino wherein the aryl contains 6 or 10 carbons and the alkyl has 1 to 6 carbons;
- (bb)-(4) alkylaminocarbonyloxy wherein the alkyl group contains 1 to 6 carbons;
- (cc) aryl containing 6, 10 or 12 carbons (e.g., phenyl, naphthyl, biphenyl);
- (cc)-(1) aryloxy containing 6, 10 or 12 carbons;
- (dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (dd)-(1) aryloxy containing 6, 10 or 12 carbons and substituted on carbon by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);
- (ee)-(1) cycloalkyloxy containing from 3 to 15 carbons;
- (ff) an aliphatic heterocyclic group of at least 4 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen (e.g., morpholine, piperazine), wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 1 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbon atoms, an aralkyloxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an

alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;

(ff)-(1) an aliphatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon atom of the aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, (e.g., morpholine, piperazine), wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 1 to 6 carbons, an aryloxycarbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkyloxycarbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;

(gg) an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and (2) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbon atoms;

(gg)-(1) an aromatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon of an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and (2) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbon atoms;

(hh) alkylureido wherein the alkyl group contains from 1 to 6 carbon atoms;

(hh)-(1) cycloalkylureido wherein the alkyl group contains 3 to 15 carbons;

(ii) aralkylureido wherein the aralkyl group contains from 7 to 13 carbons;

(ji) arylureido wherein the aryl group contains 6, 10 or 12 carbons;

(ji)-(1) arylureido wherein the aryl group contains 6, 10 or 12 carbons and is substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

For nitrogen:

(a) alkyl of 1 to 3 carbons;

(b) alkanoyl containing from 2 to 6 carbon atoms;

(c) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;

(d) aralkanoyl containing 8 to 14 carbons;

(e) formyl;

(f) an aliphatic heterocyclic group wherein the amino link is bonded directly to a carbon of an aliphatic heterocyclic group defined in (ff) for the carbon substituents;

(g) an aromatic heterocyclic group wherein the amino link is bonded directly to a carbon of the aromatic heterocyclic group defined in (gg) for the carbon substituents.

(IV) an aryl group containing 6, 10 or 12 carbons;

(V) an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkoxycarbonyl containing from 2 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

(VI) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);

(VI)-(1) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl), substituted by a member selected from the group consisting of carboxy and alkoxycarbonyl wherein the alkoxy group contains 1 to 4 carbons;

(VII) an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, (e.g., morpholine, piperazine) which may be substituted at any nitrogen with a member selected from the group consisting of an alkyl group containing from 1 to 6 carbon atoms, an alkanoyl group containing from 1 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkoxycarbonyl group wherein the aralkyl group contains from 7 to 13 carbons and an alkoxycarbonyl group containing from 2 to 7 carbons, provided that when A is OCO or NHCO then A must be bonded to a carbon atom of the aliphatic heterocyclic group;

(VIII) an aromatic heterocyclic group containing (a) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen, and (b) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted at any carbon atom with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, and provided further that any nitrogen may be substituted by an alkyl group containing from 1 to 6 carbons, provided that when A is OCO or NHCO then A must be bonded to a carbon of the aromatic heterocycle;

(IX) an alkenyl group of 2 to 10 carbons, having at least one double bond; and

(X) an alkenyl group of 2 to 10 carbons, having at least one double bond and substituted by a member selected from the group consisting of

(a) aryl of 6 or 10 carbons;

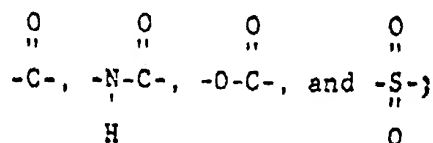
(b) aryl of 6 or 10 carbons substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro, and

(c) ureidocarbonyl.

R⁴ and R⁶ are independently selected from hydrogen or methyl;

n is 0, 1 or 2; and

A is selected from the group consisting of



or

where appropriate, the acid- and base-addition salts thereof; and provided that:

(1) alkyls may be straight or branched chain;

(2) no carbon of an alkyl may be directly bonded to two heteroatoms;

(3) no heteroatom may be directly bonded to a sulfur, nitrogen or oxygen; and

(4) alkenyls of IX and X for R³ may not be 1,1-disubstituted, and a carbon of a double bond may not be directly bonded to an oxygen or nitrogen.

2. A compound as claimed in Claim 1 wherein:

R¹ is an alkyl group containing 3 carbons;

R² and R⁵ are each selected independently from the group consisting of:

(I) an alkyl group containing from 1 to 4 carbons;

(II) an alkyl group containing from 1 to 4 carbons substituted by at least one member selected from the group consisting of:

(e) alkanoyl containing from 1 to 3 carbons;

(f) arylcarbonyl wherein the aryl contains 6 or 10 carbons;

- (g) aralkanoyl containing 8 carbons;
 (h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;
 (i) alkylcarbonylamino wherein the alkyl group contains from 1 to 2 carbons;
 (j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 2 carbons;
 5 (k) arylcarbonylamino wherein the aryl group contains 6 carbons;
 (l) aralkylcarbonylamino wherein the aralkyl group contains 7 carbons;
 (m) arylaminocarbonyl wherein the aryl group contains 6 carbons;
 (n) aralkylaminocarbonyl wherein the aralkyl group contains 7 carbons;
 (o) carboxy;
 10 (p) aryloxy carbonyl wherein the aryl group contains 6 carbons;
 (q) aralkoxy carbonyl wherein the aralkoxy group contains 7 carbons;
 (r) alkanoyloxy containing from 1 to 2 carbons;
 (s) aroyloxy wherein the aryl portion contains 6 carbons;
 (t) aralkanoyloxy containing 8 carbons;
 15 (u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;
 (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;
 (w) arylsulfonamido wherein the aryl group contains 6 or 10 carbons;
 (x) acylsulfonamido containing 1 to 15 carbons;
 (y) alkoxy carbonyl wherein the alkoxy group contains from 1 to 2 carbons;
 20 (z) aralkoxy carbonylamino wherein the aralkoxy group contains 7 carbons;
 (as) aryloxy carbonylamino wherein the aryloxy group contains 6 carbons;
 (bb) alkoxy carbonylamino wherein the alkyloxy group contains from 1 to 3 carbons;
 (cc) aryl containing 6 or 10 carbons;
 (dd) aryl containing 6 or 10 carbons and substituted by 1 to 3 members selected from the group
 25 consisting of chloro, bromo, iodo, fluoro, trifluoromethyl, hydroxy, alkyl (1 to 2 carbons), alkoxy (1 to 2 carbons), alkoxy carbonyl (2 to 3 carbons), carboxy, 5-tetrazolo and acylsulfonamido (1 to 15 carbons);
 (ee) cycloalkyl containing from 3 to 15 carbons;
 (ff) alkylureido wherein the alkyl group contains from 1 to 2 carbons;
 30 (gg) aralkylureido wherein the aralkyl group contains 7 carbons;
 (hh) arylureido wherein the aryl group contains 6 or 10 carbons; and
 (III) an aryl group of 6 carbons.
- R³ is selected from the group consisting of:
- 35 (I) an alkyl group containing from 1 to 12 carbons;
 (II) an alkyl group containing from 1 to 12 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen;
 (III) an alkyl group containing from 1 to 12 carbons and, optionally, 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, and substituted on at least one of carbon or nitrogen by 1 to 3 members selected independently from the group
 40 consisting of:
- For carbon:
- (e) alkanoyl containing from 1 to 6 carbons;
 (f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;
 (g) aralkanoyl containing 8 to 13 carbons;
 45 (h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;
 (i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;
 (j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;
 (k) arylcarbonylamino wherein the aryl group contains 6 or 10 carbons;
 (k)-(1) arylcarbonylamino wherein the aryl group contains 6 or 10 carbons and is substituted by a
 50 member selected from carboxy, alkoxy carbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido containing 1 to 15 carbons;
 (l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;
 (l)-(1) aralkylcarbonylamino wherein the aralkyl group contains 7 to 13 carbons and is substituted by a member selected from carboxy, alkoxy carbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido containing 1 to 15 carbons;
 55 (m) arylaminocarbonyl wherein the aryl group contains 6 or 10 carbons;
 (n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;
 (o) carboxy;

- (p) aryloxy carbonyl wherein the aryl group contains 6 or 10 carbons;
 (q) aralkoxycarbonyl wherein the aralkoxy group contains from 7 to 13 carbons;
 (r) alkanoyloxy containing from 2 to 3 carbons;
 (s) aroyloxy wherein the aryl portion contains 6 or 10 carbons;
 5 (t) aralkanoyloxy containing from 8 to 13 carbons;
 (u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;
 (u)-(1) cycloalkylsulfonamido wherein the cycloalkyl portion contains 3 to 15 carbons;
 (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;
 (w) arylsulfonamido wherein the aryl group contains 6 or 10 carbons;
 10 (x) acylsulfonamido containing 1 to 15 carbons;
 (y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 3 carbons;
 (z) aralkoxycarbonylamino wherein the aralkoxy group contains from 8 to 13 carbons;
 (z)-(1) aralkylaminocarbonyloxy wherein the aralkyl group contains 7 to 13 carbons;
 (z)-(2) aryloxy wherein the aryl contains 6, 10 or 12 carbons;
 15 (z)-(3) aryloxy wherein the aryl contains 6, 10 or 12 carbons and is substituted by a member selected from aminocarbonyl, aminocarbonylalkyl where the alkyl has 1 to 3 carbons, alkoxycarbonyl having 2 to 4 carbons, and carboxy;
 (aa) aryloxy carbonylamino wherein the aryloxy group contains 6 or 10 carbons;
 (aa)-(1) arylaminocarbonyloxy wherein the aryl group contains 6 or 10 carbons;
 20 (bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 6 carbons;
 (bb)-(1) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons and is optionally bonded to a carbon of an aromatic heterocyclic group as described in (gg) under R³;
 (bb)-(2) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons substituted by an aliphatic heterocyclic group as described in (ff) under R³;
 25 (bb)-(3) aryloxyalkylcarbonylamino wherein the aryl contains 6 or 10 carbons and the alkyl has 1 to 6 carbons;
 (bb)-(4) alkylaminocarbonyloxy wherein the alkyl group contains 1 to 6 carbons;
 (cc) aryl containing 6 or 10 carbons;
 (cc)-(1) aryloxy containing 6 or 10 carbons;
 30 (dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (1 to 15 carbons);
 (dd)-(1) aryloxy containing 6, 10 or 12 carbons and substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, acylsulfonamido (1 to 15 carbons), aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl and 5-tetrazolo;
 35 (ee) cycloalkyl containing from 3 to 15 carbons;
 (ee)-(1) cycloalkyloxy containing from 3 to 15 carbons;
 40 (ff) an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 2 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkyloxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;
 45 (ff)-(1) an aliphatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon of an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 2 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkyloxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;
 50 (gg) an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen

and oxygen and (2) from 1 to 2 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing methyl, alkoxy containing from 1 to 2 carbons, alkanoyl containing from 2 to 3 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbons;

(gg)-(1) an aromatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon atom of an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and (2) from 1 to 2 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, alkoxy containing from 1 to 2 carbons, alkanoyl containing from 2 to 3 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbons;

(hh) alkylureido wherein the alkyl group contains from 1 to 6 carbons;

(hh)-(1) cycloalkylureido wherein the alkyl group contains 3 to 15 carbons;

(ii) aralkylureido wherein the aralkyl group contains from 7 to 13 carbons;

(jj) arylureido wherein the aryl group contains 6 or 10 carbons;

(jj)-(1) arylureido wherein the aryl group contains 6 or 10 carbons and is substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, acylsulfonamido (1 to 15 carbons), aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl and 5-tetrazolo;

For nitrogen:

(a) alkyl of 1 to 3 carbons;

(b) alkanoyl containing from 2 to 6 carbons;

(c) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;

(d) aralkanoyl containing 8 to 13 carbons;

(e) formyl;

(f) an aliphatic heterocyclic amino group wherein the amino link is bonded directly to a carbon of an aliphatic heterocyclic group defined in (ff) for the carbon substituents;

(g) an aromatic heterocyclic amino group wherein the amino link is bonded directly to a carbon of the aromatic heterocyclic group defined in (gg) for the carbon substituents.

(IV) an aryl group containing 6 or 10 carbons;

(V) an aryl group containing 6 or 10 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkoxycarbonyl containing from 2 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons;

(VI) a cycloalkyl group containing from 3 to 15 carbons;

(VI)-(1) a cycloalkyl group containing from 3 to 15 carbons, substituted by a member selected from the group consisting of carbon and alkoxycarbonyl wherein the alkoxy group contains 1 to 4 carbons;

(VII) an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, which may be substituted at any nitrogen with a member selected from the group consisting of methyl, an alkanoyl group containing from 2 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6 or 10 carbons, an aralkoxycarbonyl group wherein the aralkyl group contains 7 carbons and an alkoxycarbonyl group containing from 2 to 3 carbons, provided that when A is OCO or NHCO, then A must be bonded to a carbon of the aliphatic heterocyclic group;

(VIII) an aromatic heterocyclic group containing (a) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen, and (b) from 1 to 2 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted at any carbon atom with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, alkoxy containing from 1 to 2 carbons, alkanoyl containing from 2 to 3 carbons, carboxy, and provided further that any nitrogen may be substituted by an alkyl group containing from 1 to 6 carbons,

provided that when A is OSO or NHCO then A must be bonded to a carbon of the aromatic heterocycle;

(IX) in alkenyl group of 2 to 10 carbons, having at least one double bond;

(X) an alkenyl group of 2 to 10 carbons, having at least one double bond and substituted by a member selected from the group consisting of

(a) aryl of 6 or 10 carbons;

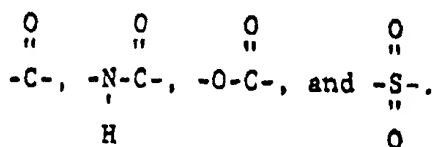
(b) aryl of 6 or 10 carbons substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, acylsulfonamido (1 to 15 carbons) and 5-tetrazolo; and

(c) ureidocarbonyl;

R⁴ and R⁶ are each hydrogen;

n = 1; and

A is selected from the group consisting of



3. A compound as claimed in Claim 1 wherein:

R¹ is isopropyl;

R² is selected from the group consisting of:

(I) an alkyl group containing 2 to 3 carbons;

(II)(q) ethyl substituted by aralkoxycarbonyl wherein the aralkoxy group contains 7 carbons;

(w) butyl substituted by an arylsulfonamido wherein the aryl portion has 6 carbons;

(x) ethyl substituted by acylsulfonamido containing 7 carbons;

(z) butyl substituted by aralkyloxycarbonylamino wherein the aralkoxy portion contains 7 carbons;

(cc) methyl substituted by an aryl containing 6 carbons; and

(III) aryl containing 6 carbons;

R³ is selected from the group consisting of:

(I) branched alkyl containing 4 carbons;

(II) an alkyl group containing 5 carbons and 2 oxygens;

(III)(k) ethyl substituted by arylcarbonylamino wherein the aryl portion contains 6 carbons;

(l) ethyl substituted by an aralkylcarbonylamino wherein the aralkyl portion contains 13 carbons;

(n) ethyl substituted by aralkylaminocarbonyl wherein the alkyl contains 7 carbons;

(o) an alkyl group containing 2 or 10 carbons and substituted by carboxy;

(w) an alkyl group containing 5 carbons and substituted by arylsulfonamido wherein the aryl portion contains 6 carbons;

(x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminoethyl)ethyl, 2-(phenylsulfonylaminoethyl)ethyl, 2-[(1-adamantyl)sulfonylaminoethyl]ethyl, and 2-[(1-naphthyl)sulfonylaminoethyl]ethyl;

(y) an alkyl group containing 2 or 10 carbons and substituted by methoxycarbonyl;

(z) an alkyl group containing 2 to 5 carbons and substituted by aralkoxycarbonyl wherein the aralkoxy portion contains 7 carbons;

(aa) an alkyl containing 5 carbons and substituted by aryloxycarbonylamino wherein the aryloxy portion contains 6 carbons;

(bb) ethyl substituted by alkoxycarbonylamino wherein the alkyl group contains 4 carbons; and an alkyl containing 5 carbons and substituted by an alkyloxycarbonylamino wherein the alkoxy group contains 2 carbons and is substituted on the terminal carbon via a direct link to a carbon atom of an aromatic heterocycle containing 5 carbons and 1 nitrogen;

(bb)-(3) a propyl group substituted by an aryloxyalkylcarbonylamino wherein the aryl group contains 6 carbons and the alkyl group is methyl;

(cc) methyl or butyl substituted by aryl containing 6 carbons; and a branched alkyl group

containing 5 carbons and substituted by 2 aryl groups each containing 6 carbons;

(dd) a member selected from the group consisting of an alkyl containing 1 or 2 carbons and substituted with an aryl containing 6 carbons wherein the aryl is further substituted by carboxy, methyl substituted by an aryl containing 6 carbons wherein the aryl is further substituted by methoxycarbonyl; ethyl substituted by an aryl containing 6 carbons wherein the aryl is further substituted by ethoxycarbonyl; and ethyl substituted by an aryl containing 6 carbons wherein the aryl is further substituted by an acylsulfonamido containing 7 carbons;

(ee) ethyl substituted by a cycloalkyl containing 10 carbons;

(ff) ethyl substituted by an aliphatic heterocycle containing 4 carbons, 1 nitrogen and 1 oxygen;

(gg) an alkyl containing 1 to 2 carbons and substituted by an aromatic heterocycle containing 4 carbons and 1 sulfur; and ethyl substituted by an aromatic heterocycle containing 5 carbons and 1 nitrogen;

(jj)-(1) an alkyl group containing 5 carbons and substituted by an arylureido wherein the aryl portion contains 6 carbons and wherein the aryl portion is further substituted by ethoxycarbonyl or carboxy;

(zz) propyl substituted by aryloxy wherein the aryl contains 6 carbons; a branched alkyl group containing 5 carbons and substituted by 2 aryloxy groups each containing 6 carbons;

(zzz) methyl or propyl substituted by an aryloxy containing 6 carbons wherein the aryloxy is further substituted by aminocarbonyl; and methyl substituted by an aryloxy containing 6 carbons wherein the aryloxy is further substituted by ethoxycarbonyl;

(IV) an aryl group containing 6 or 10 carbons;

(V) an aryl group containing 6 carbons substituted by a member selected from the group consisting of fluoro, hydroxy, carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbamoyl, an acylsulfonamido containing 2 carbons, an acylsulfonamido containing 7 carbons, an acylsulfonamido containing 11 carbons, an acylsulfonamido containing 14 carbons; an aryl group containing 6 carbons and substituted by 2 chloros; and an aryl group containing 6 carbons and substituted by one chloro and one amino;

(VI) a cycloalkyl containing 10 carbons;

(VI)-(1) a cycloalkyl containing 5 carbons and substituted by carboxy or ethoxycarbonyl; and

(X) an alkenyl group containing 2 carbons and substituted by a member selected from the group consisting of carboxy, carboxyphenyl, ethoxycarbonyl, ureidocarbonyl, acylsulfonamido, and 4-carboxyphenyl.

R⁴ is hydrogen;

R⁵ is selected from the group consisting of:

(I) n-butyl;

(II)(q) ethyl substituted by aralkoxycarbonyl wherein the aralkoxy contains 7 carbons; and

(II)(z) butyl substituted by aralkyloxycarbonylamino wherein the aralkyl group contains 7 carbons;

A is as defined above; and

n = 1.

4. A compound as claimed in Claim 1 selected from the group consisting of:

1) 3S(orR)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

2) 3(RS)-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

3) 3(RS)-[(4-(Ethoxycarbonyl)phenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

4) 3(RS)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

5) 3(RS)-[(4-Phenylbutyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

6) 3(RS)-2[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

7) 3(RS)-[(4-Methoxyphenyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

8) 3(RS)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

9) 3(RS)-[(Phenylmethoxy)carbonyl]-L-phenylalanyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

10) 3(RS)-[2-(Methoxycarbonyl)ethylcarbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;

- 11) 3(RS)-[(2-Carboxyethyl)carbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;
- 12) 3(RS)-[(Phenylmethoxy)carbonyl]-L-alpha-glutamyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide phenylmethyl ester;
- 5 13) 3(RS)-N²-[2-(Methoxycarbonyl)ethylcarbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;
- 14) 3(RS)-N²-[(2-Carboxyethyl)carbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;
- 15) 3S(orR)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;
- 10 16) 3(RS)-[1-Naphthylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 17) 3(RS)-[4-(Methylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 18) 3(RS)-[2-(4-Morpholinyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 15 19) 3(RS)-[(2,4-Dichlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 20) 3(RS)-Phenoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 21) 3(RS)-[2-(2-Pyridyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 20 22) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 23) 3(RS)-[2-(3-Thiophenyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 25 24) 3(RS)-(Phenylmethoxycarbonyl)-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 25) 3(RS)-(Phenoxycarbonyl)-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 26) 3(RS)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 30 27) 3(RS)-[2-(Tricyclo[3.3.1.1^{3,7}]-dec-1-yl)ethoxycarbonyl]-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 28) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 35 29) 3(RS)-N⁶-Phenylmethoxycarbonyl-N²-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 30) 3(RS)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 31) 3(RS)-Phenylaminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 40 32) 3(RS)-[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 33) 3(RS)-N²-(4-Hydroxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 34) 3(RS)-(4-Hydroxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 45 35) 3(RS)-(Tricyclo[3.3.1.1^{3,7}]-dec-1-yl)sulfonyl-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 36) 3(RS)-(4-Methoxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 50 37) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 38) 3(RS)-(4-Methoxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 39) 3(RS)-[E-3-(4-Ethoxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 55 40) 3(RS)-(2-Ethoxycarbonylphenyl)aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 41) 3(RS)-4-[(4-Nitrophenyl)sulfonylaminocarbonyl]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-

methyl-2-oxopentyl)]-L-prolinamide;

42) 3(RS)-Phenylmethoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide phenylmethyl ester;

43) 3S(or R)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

44) 3(RS)-Phenylmethoxycarbonyl-L-[5-(phenylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

45) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

46) 3(RS)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

47) 3(RS)-4-(1-Naphthylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

48) 3(RS)-[2-(4-Aminocarbonylphenoxy)-1-oxoethyl]-L-Valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

49) 3(RS)-(4-Hydroxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

50) 3(RS)-[4-[4-(2-Amino-2-oxoethyl)phenoxy]-1-oxobutyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

51) 3(RS)-E-[3-(4-Hydroxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

52) 3(RS)-[2-(4-Ethoxycarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

53) 3(RS)-[3-(4-Ethoxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

54) 3(RS)-4-Hydroxybenzoyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

55) 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

56) 3(RS)-[3-(4-Hydroxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

57) 3(RS)-[3-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

58) 3(RS)-E-[3-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

59) 3(RS)-[1-[4-[(4-Bromophenyl)sulfonyl]phenylmethyl]aminocarbonyl]phenyl]-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

60) 3R(or S)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

61) 3S(or R)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

62) 3S(or R)-Phenylmethoxycarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

63) 3S(or R)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

64) 3S(or R)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

65) 3S(or R)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

66) 3S(or R)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

67) 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

68) 3(RS)-N²,N⁶-Di(phenylmethoxycarbonyl)-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

69) 3(RS)-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

70) 3(RS)-[4-(Methylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

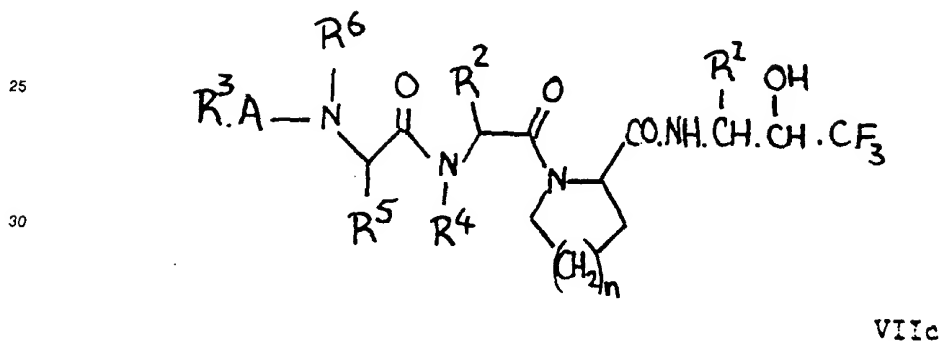
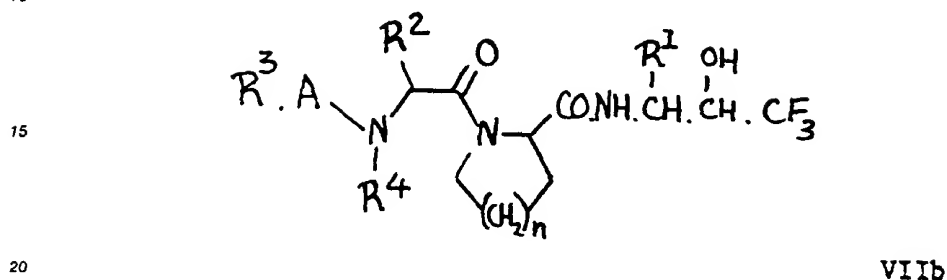
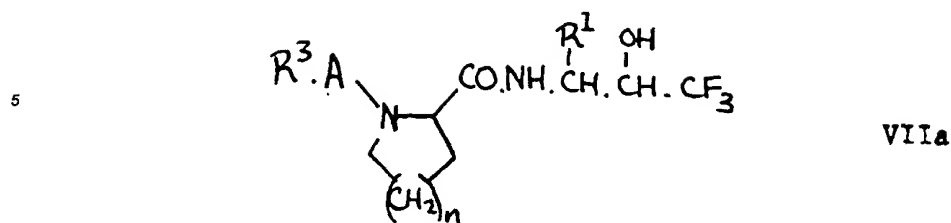
- 71) 3(RS)-N²-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-N⁶-phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; and
 72) 3(RS)-[1,4-Dioxo-4-[(tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonylamino]butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide.

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5. A compound as claimed in Claim 4 selected from the group consisting of:

- 1) 3(RS)-[(4-Carboxyphenyl)aminocarbonyl]-L-, valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;
- 2) 3(RS)-[(2-Carboxyethyl)carbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;
- 3) 3(RS)-N²-[(2-Carboxyethyl)carbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide;
- 4) 3(RS)-[4-(Methylsulfonylamino)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 5) 3(RS)-[4-(Phenylsulfonylamino)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 6) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 7) 3(RS)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 8) 3(RS)-[[4-[(1-Naphthylsulfonyl)aminocarbonyl] phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 9) 3(RS)-N²-(4-Hydroxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 10) 3(RS)-(4-Hydroxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 11) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 12) 3(RS)-4-[(4-Nitrophenyl)sulfonylamino]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 13) 3(RS)-Phenylmethoxycarbonyl-L-[5-(phenylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 14) 3(RS)-[4-(Phenylsulfonylamino)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 15) 3(RS)-[4-[(4-Bromophenyl)sulfonylamino]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 16) 3(RS)-4-(1-Naphthylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 17) 3(RS)-(4-Hydroxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 18) 3(RS)-E-[3-(4-Hydroxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 19) 3(RS)-[4-[(4-Chlorophenyl)sulfonylamino]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 20) 3(RS)-[3-(4-Hydroxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 21) 3(RS)-[3-[4-[(4-Chlorophenyl)sulfonylamino]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 22) 3(RS)-E-[3-(4-[(4-Chlorophenyl)sulfonylamino]phenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 23) 3S(or R)-[4-(Phenylsulfonylamino)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 24) 3S(or R)-[4-[(4-Bromophenyl)sulfonylamino]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 25) 3S(or R)-[4-[(4-Chlorophenyl)sulfonylamino]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
- 26) 3S(or R)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;

- 27) 3(RS)-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
 28) 3(RS)-[4-(Methylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; and
 5 29) 3(RS)-N²-[1,4-Dioxo-4-(phenylsulfonylamido)butyl]-N⁶-phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide.
6. A compound as claimed in Claim 5 selected from the group consisting of:
 1) 3(RS)-[4-[(1-Naphthylsulfonyl)aminocarbonyl] phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
 10 2) 3(RS)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
 3) 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide;
 15 4) 3S(or R)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; and
 5) 3S(or R)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide.
- 20 7. A compound as claimed in Claim 1 wherein said acid addition salt is one formed with hydrochloric, hydrobromic, sulfuric, nitric, citric, maleic, fumeric or acetic acid.
8. A compound as claimed in Claim 1 wherein said base addition salt is one formed with an alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkaline earth hydroxide or an organic amine salt.
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9. A process for producing the compounds as claimed in any one of Claims 1 through 8 comprising oxidizing a compound of formula VIIa, VIIb or VIIc
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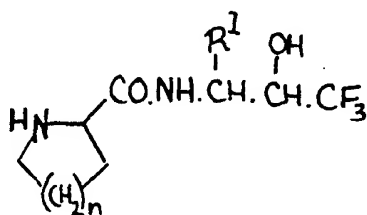
35 to form a first compound of formula Ia, Ib or Ic,

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10. A process as claimed in Claim 9 which comprises an oxidation using a member selected from a group consisting of the following:
- (a) oxalylchloride, dimethyl sulfoxide, and a tertiary amine in methylene chloride;
 - (b) acetic anhydride and dimethyl sulfoxide;
 - (c) chromium trioxide-pyridine complex in methylene chloride; and
 - (d) Dess-Martin periodinane in methylene chloride.
- 45
11. A process as claimed in Claim 10 wherein said oxidation comprises using Dess-Martin periodinane in methylene chloride.
- 50
12. The process of Claim 9 further comprising forming a second compound of formula Ia, Ib, or Ic containing a carboxy group in R², R³, or R⁵ from said first compound of formula Ia, Ib, or Ic, respectively, wherein said first compound contains a carboxylic acid ester group in R², R³ or R⁵, wherein said method comprises converting said carboxylic acid ester group into the corresponding carboxy group.
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13. A process as claimed in Claim 12 which comprises converting said carboxylic acid ester group into the corresponding carboxy group by hydrolysis.
14. The process of Claim 9 or Claim 12 further comprising forming a third compound of formula Ia, Ib or Ic

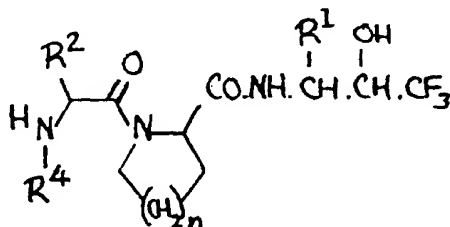
containing a sulfonylaminocarbonyl group in R^2 , R^3 or R^5 from said first or said second compound of formula Ia, Ib or Ic, respectively, wherein said first or said second compound contains a carboxy group in R^2 , R^3 , or R^5 by coupling said carboxy group with the amino group of a sulfonamide.

- 5 15. A process as claimed in Claim 14 which comprises a coupling method selected from using a member of a group consisting of the following:
- (a) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 4-dimethylaminopyridine in methylene chloride; and
- (b) 1,3-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in methylene chloride.
- 10 16. A pharmaceutical composition comprising a compound of Claim 1, or a salt thereof, in association with a non-toxic pharmaceutically-acceptable diluent or carrier.
17. A compound of the formula IVa, IVb or IVc :-

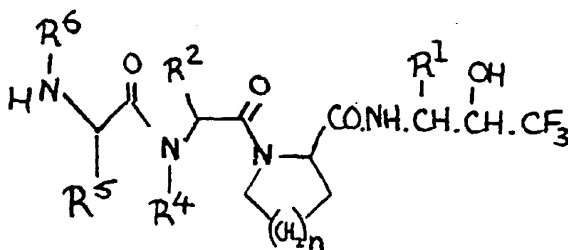
IVa



IVb



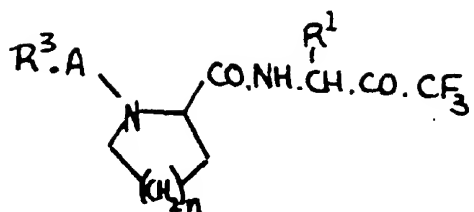
IVc



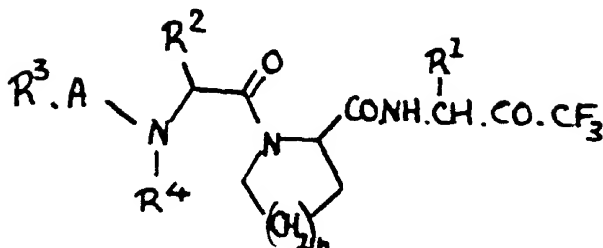
wherein R^1 , R^2 , R^4 , R^5 , R^6 and n have any of the meanings defined in Claim 1.

Claims for the following Contracting State : AT

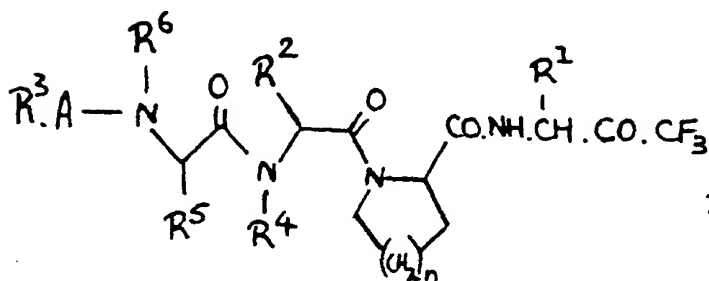
- 50 1. A process for producing a compound of formula Ia, Ib or Ic



Ia



Ib



Ic

wherein

R¹ is an alkyl group containing from 1 to 5 carbon atoms, and more preferably from 2 to 5 carbons;R² and R⁵ are each selected independently from the group consisting of:

(I) an alkyl group containing from 1 to 10 carbons;

(II) an alkyl group containing from 1 to 6 carbon atoms substituted by at least one member selected from the group consisting of:

(a) hydroxy;

(b) amino;

(c) alkylamino containing from 1 to 6 carbons;

(d) dialkylamino wherein each alkyl group contains from 1 to 6 carbons;

(e) alkanoyl containing from 1 to 6 carbons;

(f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;

(g) aralkanoyl containing 8 to 13 carbons;

(h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;

(i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;

(j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;

(k) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons;

(l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;

(m) arylaminocarbonyl wherein the aryl group contains 6, 10 or 12 carbons;

(n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;

(o) carboxy;

(p) aryloxy carbonyl wherein the aryl group contains 6, 10 or 12 carbons;

(q) aralkoxy carbonyl wherein the aralkoxy group contains from 7 to 13 carbons;

(r) alkanoyloxy containing from 1 to 6 carbons;

(s) aroyloxy wherein the aryl portion contains 6, 10 or 12 carbons;

(t) aralkanoyloxy containing from 8 to 14 carbons;

(u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;

- (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;
- (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons;
- (x) acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 6 carbons;
- (z) aralkoxycarbonylamino wherein the aralkoxy group contains from 8 to 13 carbons (e.g., benzyloxycarbonyl amino);
- (aa) aryloxycarbonylamino wherein the aryloxy group contains 6, 10 or 12 carbons;
- (bb) alkoxycarbonylamino wherein the alkyloxy group contains from 1 to 6 carbons;
- (cc) aryl containing 6, 10 or 12 carbons (e.g., phenyl, biphenyl, naphthyl);
- (dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members selected from the group consisting of chloro, bromo, iodo, fluoro, trifluoromethyl, hydroxy, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl).
- (ff) alkylureido wherein the alkyl group contains from 1 to 6 carbons;
- (gg) aralkylureido wherein the aralkyl group contains from 8 to 13 carbons;
- (hh) arylureido wherein the aryl group contains 6, 10 or 12 carbons; and
- (III) an aryl group of 6 carbons, e.g. phenyl.
- R³ is selected from the group consisting of:
- (I) an alkyl group containing from 1 to 12 carbons;
- (II) an alkyl group containing from 1 to 12 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen;
- (III) an alkyl group containing from 1 to 12 carbons and, optionally, 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, and substituted on at least one of carbon or nitrogen by 1 to 3 members selected independently from the group consisting of:
- For carbon:
- (a) hydroxy, provided that it may not be on a carbon directly bonded to A;
- (b) amino, provided that it may not be on a carbon directly bonded to A;
- (c) alkylamino containing from 1 to 6 carbons, provided that it may not be on a carbon directly bonded to A;
- (d) dialkylamino wherein each alkyl group contains from 1 to 6 carbons, provided that it may not be on a carbon directly bonded to A;
- (e) alkanoyl containing from 1 to 6 carbons;
- (f) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;
- (g) aralkanoyl containing 8 to 13 carbons;
- (h) amido which may be attached to the alkyl group via either a nitrogen or carbon of said amido;
- (i) alkylcarbonylamino wherein the alkyl group contains from 1 to 6 carbons;
- (j) alkylaminocarbonyl wherein the alkyl group contains from 1 to 6 carbons;
- (k) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons;
- (k)-(1) arylcarbonylamino wherein the aryl group contains 6, 10 or 12 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (l) aralkylcarbonylamino wherein the aralkyl group contains from 7 to 13 carbons;
- (l)-(1) aralkylcarbonylamino wherein the aralkyl group contains 7 to 13 carbons and is substituted by a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- (m) arylaminocarbonyl wherein the aryl group contains 6, 10 or 12 carbons;
- (n) aralkylaminocarbonyl wherein the aralkyl group contains from 7 to 13 carbons;

- (o) carboxy;
- (p) aryloxy carbonyl wherein the aryl group contains 6, 10 or 12 carbons;
- (q) aralkoxy carbonyl wherein the aralkoxy group contains from 7 to 13 carbons;
- (r) alkanoyloxy containing from 1 to 6 carbons;
- 5 (s) aroyloxy wherein the aryl portion contains 6, 10 or 12 carbons;
- (t) aralkanoyloxy containing from 8 to 13 carbons;
- (u) alkylsulfonamido wherein the alkyl group contains from 1 to 6 carbons;
- (u)-(1) cycloalkylsulfonamido wherein the cycloalkyl portion contains 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);
- 10 (v) aralkylsulfonamido wherein the aralkyl group contains from 7 to 13 carbons;
- (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons;
- (x) acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide, and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- 15 (y) alkoxycarbonyl wherein the alkoxy group contains from 1 to 6 carbons;
- (z) aralkoxy carbonylamino wherein the aralkoxy group contains from 8 to 13 carbons (e.g., benzyloxy carbonylamino);
- (z)-(1) aralkylaminocarbonyloxy wherein the aralkyl group contains 8 to 13 carbons;
- 20 (z)-(2) aryloxy wherein the aryl contains 6, 10 or 12 carbons;
- (z)-(3) aryloxy wherein the aryl contains 6, 10 or 12 carbons and is substituted by a member selected from aminocarbonyl, aminocarbonylalkyl where the alkyl has 1 to 3 carbons, alkoxycarbonyl having 1 to 3 carbons, and carboxy;
- (aa) aryloxy carbonylamino wherein the aryloxy group contains 6, 10 or 12 carbons;
- 25 (aa)-(1) arylaminocarbonyloxy therein the aryl group contains 6, 10 or 12 carbons;
- (bb) alkoxycarbonylamino wherein the alkoxy group contains from 1 to 6 carbons;
- (bb)-(1) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons and is optionally bonded on carbon to a carbon of an aromatic heterocyclic group as described in (gg) under R³;
- (bb)-(2) alkoxycarbonylamino wherein the alkoxy group contains 1 to 6 carbons substituted by an aliphatic heterocyclic group as described in (ff) under R³;
- 30 (bb)-(3) aryloxyalkyl carbonylamino wherein the aryl contains 6 or 10 carbons and the alkyl has 1 to 6 carbons;
- (bb)-(4) alkylaminocarbonyloxy wherein the alkyl group contains 1 to 6 carbons;
- (cc) aryl containing 6, 10 or 12 carbons (e.g., phenyl, naphthyl, biphenyl);
- 35 (cc)-(1) aryloxy containing 6, 10 or 12 carbons;
- (dd) aryl containing 6, 10 or 12 carbons and substituted by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- 40 (dd)-(1) aryloxy containing 6, 10 or 12 carbons and substituted on carbon by 1 to 3 members independently selected from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;
- 45 (ee) cycloalkyl containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);
- (ee)-(1) cycloalkyloxy containing from 3 to 15 carbons;
- (ff) an aliphatic heterocyclic group of at least 4 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen (e.g., morpholine, piperazine), wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 1 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbon atoms, an aralkyloxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an
- 50
- 55

alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;

(ff)-(1) an aliphatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon atom of the aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, (e.g., morpholine, piperazine), wherein the aliphatic heterocyclic group may optionally contain 1 or 2 double bond(s), which aliphatic heterocyclic group may be substituted at any nitrogen with an alkyl group containing from 1 to 6 carbons, an alkanoyl group containing from 1 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkyloxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons or an alkoxycarbonyl group wherein the alkyl group contains from 1 to 6 carbons;

(gg) an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and (2) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbon atoms;

(gg)-(1) an aromatic heterocyclic oxy group wherein the oxy link is bonded directly to a carbon of an aromatic heterocyclic group containing (1) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen and (2) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, aminocarbonylalkyl (2 to 6 carbons) and aminocarbonyl, and provided further that any nitrogen atom may be substituted by an alkyl group containing from 1 to 6 carbons;

(hh) alkylureido wherein the alkyl group contains from 1 to 6 carbon atoms;

(hh)-(1) cycloalkylureido wherein the alkyl group contains 3 to 15 carbons;

(ii) aralkylureido wherein the aralkyl group contains from 7 to 13 carbons;

(ji) arylureido wherein the aryl group contains 6, 10 or 12 carbons;

(ji)-(1) arylureido wherein the aryl group contains 6, 10 or 12 carbons and is substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

For nitrogen:

(a) alkyl of 1 to 3 carbons;

(b) alkanoyl containing from 2 to 6 carbon atoms;

(c) arylcarbonyl wherein the aryl contains 6, 10 or 12 carbons;

(d) aralkanoyl containing 8 to 14 carbons;

(e) formyl;

(f) an aliphatic heterocyclic group wherein the amino link is bonded directly to a carbon of an aliphatic heterocyclic group defined in (ff) for the carbon substituents;

(g) an aromatic heterocyclic group wherein the amino link is bonded directly to a carbon of the aromatic heterocyclic group defined in (gg) for the carbon substituents.

(IV) an aryl group containing 6, 10 or 12 carbons;

(V) an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkoxycarbonyl containing from 2 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro;

(VI) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl);

(VI)-(1) a cycloalkyl group containing from 3 to 15 carbons (e.g., cyclohexyl, adamantyl, norbornyl), substituted by a member selected from the group consisting of carboxy and alkoxy carbonyl wherein the alkoxy group contains 1 to 4 carbons;

(VII) an aliphatic heterocyclic group of at least 5 atoms containing from 1 to 5 carbons and from 1 to 4 hetero atoms each of which is selected independently from the group consisting of nitrogen and oxygen, (e.g., morpholine, piperazine) which may be substituted at any nitrogen with a member selected from the group consisting of an alkyl group containing from 1 to 6 carbon atoms, an alkanoyl group containing from 1 to 6 carbons, an aryloxy carbonyl group wherein the aryl group contains 6, 10 or 12 carbons, an aralkoxy carbonyl group wherein the aralkyl group contains from 7 to 13 carbons and an alkoxy carbonyl group containing from 2 to 7 carbons, provided that when A is OCO or NHCO then A must be bonded to a carbon atom of the aliphatic heterocyclic group;

(VIII) an aromatic heterocyclic group containing (a) from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is selected independently from the group consisting of sulfur, nitrogen and oxygen, and (b) from 1 to 3 five or six-membered rings at least one of which is aromatic, and optionally, wherein up to 3 carbons of the aromatic ring(s) may be substituted at any carbon atom with a member of the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, alkanoyl containing from 2 to 6 carbons, carboxy, and provided further that any nitrogen may be substituted by an alkyl group containing from 1 to 6 carbons, provided that when A is OCO or NHCO then A must be bonded to a carbon of the aromatic heterocycle;

(IX) an alkenyl group of 2 to 10 carbons, having at least one double bond; and

(X) an alkenyl group of 2 to 10 carbons, having at least one double bond and substituted by a member selected from the group consisting of

(a) aryl of 6 or 10 carbons;

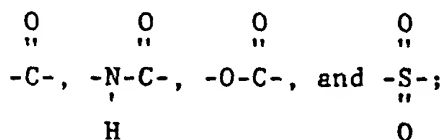
(b) aryl of 6 or 10 carbons substituted by 1 to 3 members selected independently from the group consisting of chloro, bromo, iodo, fluoro, hydroxy, trifluoromethyl, alkyl (1 to 6 carbons), alkoxy (1 to 6 carbons), alkoxy carbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and sulfonylaminocarbonyl) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and

(c) ureidocarbonyl.

R⁴ and R⁵ are independently selected from hydrogen or methyl;

n is 0, 1 or 2; and

A is selected from the group consisting of



and

where appropriate, the acid- and base-addition salts thereof and provided that:

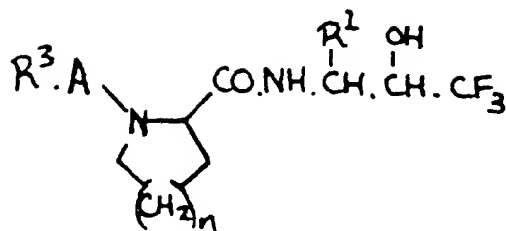
(1) alkyls may be straight or branched chain;

(2) no carbon of an alkyl may be directly bonded to two heteroatoms;

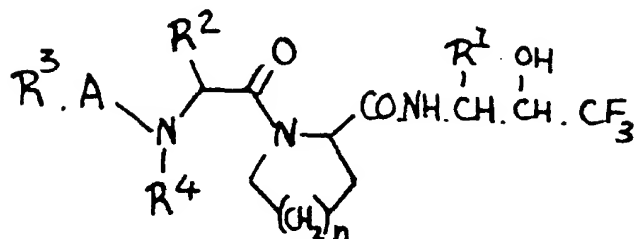
(3) no heteroatom may be directly bonded to a sulfur, nitrogen or oxygen; and

(4) alkenyls of IX and X for R³ may not be 1,1-disubstituted, and a carbon of a double bond may not be directly bonded to an oxygen or nitrogen

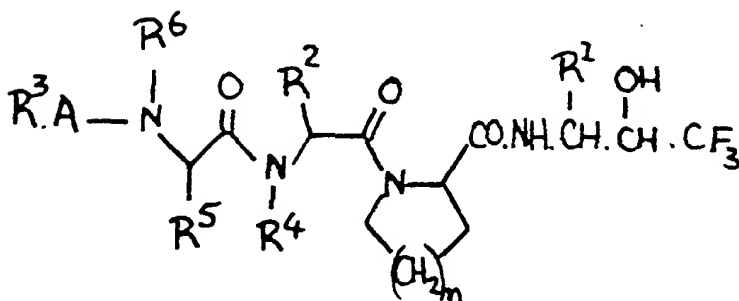
wherein said process comprises oxidizing a compound of formula VIIa, VIIb, or VIIc, respectively.



VIIa



VIIb



VIIc

2. A process as claimed in Claim 1 which comprises an oxidation selected from a group consisting of the following:
 - (a) oxalylchloride, dimethyl sulfoxide, and a tertiary amine in methylene chloride;
 - (b) acetic anhydride and dimethyl sulfoxide;
 - (c) chromium trioxide-pyridine complex in methylene chloride; and
 - (d) Dess-Martin periodinane in methylene chloride.
3. A process as claimed in Claim 1 or Claim 2 wherein said oxidation comprises using Dess-Martin periodinane in methylene chloride.
4. The process of Claim 1 further comprising forming a second compound of formula Ia, Ib, or Ic containing a carboxy group in R², R³, or R⁵ from said first compound of formula Ia, Ib, or Ic, respectively, wherein said first compound contains a carboxylic acid ester group in R², R³ or R⁵ wherein said method comprises converting said carboxylic acid ester group into the corresponding carboxy group.
5. A process as claimed in Claim 4 which comprises converting said carboxylic acid ester group into the corresponding carboxy group by hydrolysis.

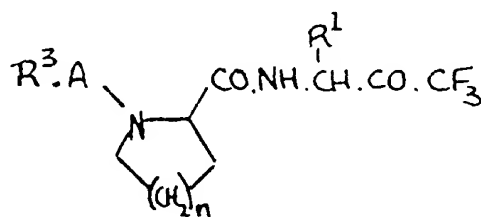
6. The process of Claim 1 or Claim 4 further comprising forming a third compound of formula Ia, Ib or Ic containing a sulfonylaminocarbonyl group in R^2 , R^3 or R^5 from said first or said second compound of formula Ia, Ib or Ic, respectively, wherein said first or said second compound contains a carboxy group in R^2 , R^3 , or R^5 by coupling said carboxy group with the amino group of a sulfonamide.

7. A process as claimed in Claim 6 which comprises a coupling selected from using a member of a group consisting of the following:
- (a) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 4-dimethylaminopyridine in methylene chloride; and
 - (b) 1,3-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in methylene chloride.

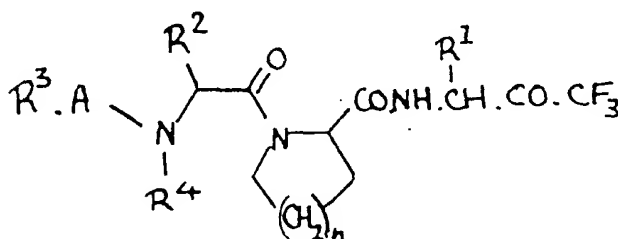
Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

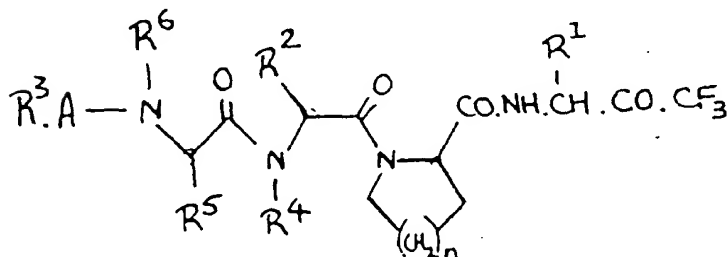
1. Compose de formule Ia, Ib ou Ic :



Ia



Ib



Ic

dans laquelle

R^1 est un groupe alkyle contenant 1 à 5 atomes de carbone et de préférence 2 à 5 atomes de carbone ;

R^2 et R^5 sont choisis chacun, indépendamment, dans le groupe comprenant :

- (I) un groupe alkyle contenant 1 à 10 atomes de carbone ;
- (II) un groupe alkyle contenant 1 à 6 atomes de carbone, substitué par au moins un représentant du groupe constitué de :

- (a) hydroxy ;
- (b) amino ;
- (c) alkylamino contenant 1 à 6 atomes de carbone ;
- (d) dialkylamino contenant dans chaque groupe alkyle 1 à 6 atomes de carbone ;

- (e) alcanoyloxy contenant 1 à 6 atomes de carbone ;
 (f) arylcarbonyloxy dont le radical aryle contient 6, 10 ou 12 atomes de carbone ;
 (g) aralcanoyloxy contenant 8 à 13 atomes de carbone ;
 (h) amido qui peut être attaché au groupe alkyle par un atome d'azote ou de carbone dudit
 5 groupe amido ;
 (i) alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (j) alkylaminocarbonyloxy dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (k) arylcarbonylamino dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 (l) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
 10 (m) arylaminocarbonyloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 (n) aralkylaminocarbonyloxy dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
 (o) carboxy ;
 (p) aryloxydont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 (q) aralkoxydont le groupe aralkoxy contient 7 à 13 atomes de carbone ;
 15 (r) alcanoyloxy contenant 1 à 6 atomes de carbone ;
 (s) aryloxy dont la portion aryle contient 6, 10 ou 12 atomes de carbone ;
 (t) aralcanoyloxy contenant 8 à 14 atomes de carbone ;
 (u) alkylsulfonamido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (v) aralkylsulfonamido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
 20 (w) arylsulfonamido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 (x) acylsulfonamido (c'est-à-dire acylaminosulfonyl et sulfonaminocarbonyl) comprenant un
 groupe acylsulfonamido dont le groupe acyle contient 1 à 7 atomes de carbone lorsqu'il occupe
 la position terminale de l'acylsulfonamide et sous réserve que lorsque le groupe acylsulfonamido
 25 contient un groupe aryle, le groupe aryle puisse encore être substitué par un substituant choisi
 entre fluoro, chloro, bromo, iodo et nitro ;
 (y) alkoxydont le groupe alkoxy contient 1 à 6 atomes de carbone ;
 (z) aralkoxydont le groupe aralkoxy contient 8 à 13 atomes de carbone (par
 exemple benzyloxydont le groupe benzyle contient 7 à 12 atomes de carbone) ;
 (aa) aryloxydont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 30 (bb) alkoxydont le groupe alkoxy contient 1 à 6 atomes de carbone ;
 (cc) aryle contenant 6, 10 ou 12 atomes de carbone (par exemple phényle, biphenyle, naphthyle) ;
 (dd) aryle contenant 6, 10 ou 12 atomes de carbone et substitué par 1 à 3 représentants du
 groupe comprenant les radicaux chloro, bromo, iodo, fluoro, trifluorométhyle, hydroxy, alkyle (1 à
 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxydont le groupe alkoxy contient 1 à 6
 35 atomes de carbone), carboxy, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyl et sulfonami-
 nocarbonyl (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido
 contient un radical aryle, le radical aryle puisse encore être substitué par un substituant choisi
 entre fluoro, chloro, bromo, iodo et nitro ;
 (ee) cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle,
 40 norbornyle) ;
 (ff) alkyluréido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (gg) aralkyluréido dont le groupe aralkyle contient 8 à 13 atomes de carbone ;
 (hh) aryluréido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ; et
 (iii) un groupe aryle de 6 atomes de carbone, par exemple phényle,
 45 R³ est choisi dans le groupe comprenant :
 (i) un groupe alkyle contenant 1 à 12 atomes de carbone ;
 (ii) un groupe alkyle contenant 1 à 12 atomes de carbone et 1 à 4 hétéroatomes choisis chacun
 indépendamment dans le groupe comprenant des atomes d'azote et d'oxygène ;
 (iii) un groupe alkyle contenant 1 à 12 atomes de carbone et, à titre facultatif, 1 à 4 hétéroatomes
 50 choisis chacun indépendamment dans le groupe comprenant l'azote et l'oxygène et substitué sur au
 moins l'un des atomes de carbone et d'azote par 1 à 3 représentants du groupe comprenant :
 Pour le carbone :
 (a) hydroxy, sous réserve qu'il ne puisse pas se trouver sur un atome de carbone directement lié
 à A ;
 55 (b) amino, sous réserve qu'il ne puisse pas se trouver sur un atome de carbone directement lié à
 A ;
 (c) alkylamino contenant 1 à 6 atomes de carbone, sous réserve qu'il ne puisse pas se trouver
 sur un atome de carbone directement lié à A ;

- (d) dialkylamino dont chaque groupe alkyle contient 1 à 6 atomes de carbone, sous réserve qu'il ne puisse pas se trouver sur un atome de carbone directement lié à A ;
- (e) alcanoyloxy contenant 1 à 6 atomes de carbone ;
- (f) arylcarbonyloxy dont le radical aryle contient 6, 10 ou 12 atomes de carbone ;
- 5 (g) aralcanoyloxy contenant 8 à 13 atomes de carbone ;
- (h) amido qui peut être attaché au groupe alkyle par un atome d'azote ou de carbone dudit groupe amido ;
- (i) alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone ;
- (j) alkylaminocarbonyloxy dont le groupe alkyle contient 1 à 6 atomes de carbone ;
- 10 (k) arylcarbonylamino dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (k)-(1) arylcarbonylamino dont le groupe aryle contient 6, 10 ou 12 atomes de carbone et est substitué par un substituant choisi entre carboxy, alkoxycarbonyloxy, dont le radical alkoxy comprend 1 à 3 atomes de carbone, 5-tétrazolo, et acylsulfonamido (c'est-à-dire acylaminosulfonyloxy et sulfonylaminocarbonyloxy) contenant 1 à 15 atomes de carbone et sous réserve que lorsque le
- 15 groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore porter un substituant choisi dans le groupe des substituants fluoro, chloro, bromo, iodo et nitro ;
- (l) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
- (l)-(1) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone et est substitué par un représentant du groupe des substituants carboxy, alkoxycarbonyloxy dont le radical alkoxy comprend 1 à 3 atomes de carbone, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyloxy et sulfonylaminocarbonyloxy) contenant 1 à 15 atomes de carbone et sous réserve que
- 20 lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore porter un substituant choisi dans le groupe des substituants fluoro, chloro, bromo, iodo et nitro ;
- (m) arylaminocarbonyloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- 25 (n) aralkylaminocarbonyloxy dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
- (o) carboxy ;
- (p) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (q) aralkoxy dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
- (r) alcanoyloxy contenant 1 à 6 atomes de carbone ;
- 30 (s) aryloxy dont la portion aryle contient 6, 10 ou 12 atomes de carbone ;
- (t) aralcanoyloxy contenant 8 à 13 atomes de carbone ;
- (u) alkylsulfonamido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
- (u)-(1) cycloalkylsulfonamido dont la portion cycloalkyle contient 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) ;
- 35 (v) aralkylsulfonamido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
- (w) arylsulfonamido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (x) acylsulfonamido (c'est-à-dire acylaminosulfonyloxy et sulfonylaminocarbonyloxy) (1 à 15 atomes de carbone) comprenant un groupe acylsulfonamido dont le groupe acyle contient 1 à 7 atomes de carbone lorsqu'il occupe la position terminale de l'acylsulfonamide, et sous réserve que
- 40 lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore porter un substituant choisi dans le groupe des substituants fluoro, chloro, bromo, iodo et nitro ;
- (y) alkoxycarbonyloxy dont le groupe alkoxy contient 1 à 6 atomes de carbone ;
- (z) aralkoxydont le groupe aralkyle contient 8 à 13 atomes de carbone (par exemple benzyloxydont le groupe aralkyle contient 8 à 13 atomes de carbone) ;
- 45 (z)-(1) aralkylaminocarbonyloxy dont le groupe aralkyle contient 8 à 13 atomes de carbone ;
- (z)-(2) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (z)-(3) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone et porte un représentant choisi dans le groupe des substituants aminocarbonyloxy, aminocarbonylalkyle dont le radical alkyle comprend 1 à 3 atomes de carbone, alkoxycarbonyloxy ayant 1 à 3 atomes de
- 50 carbone et carboxy ;
- (aa) aryloxydont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (aa)-(1) arylaminocarbonyloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (bb) alkoxycarbonylamino dont le groupe alkoxy contient 1 à 6 atomes de carbone ;
- (bb)-(1) alkoxycarbonylamino dont le groupe alkoxy contient 1 à 6 atomes de carbone et est
- 55 facultativement attaché par du carbone à un atome de carbone d'un groupe hétérocyclique aromatique comme décrit en (gg) pour R³ ;
- (bb)-(2) alkoxycarbonylamino dont le groupe alkoxy contient 1 à 6 atomes de carbone, substitué par un groupe hétérocyclique aliphatique comme décrit en (ff) pour R³ ;

(bb)-(3) aryloxyalkylcarbonylamino dont le groupe aryle contient 6 à 10 atomes de carbone et le groupe alkyle contient 1 à 6 atomes de carbone ;

(bb)-(4) alkylaminocarbonyloxy dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(cc) aryle contenant 6, 10 ou 12 atomes de carbone (par exemple phényle, naphthyle, biphényle) ;

5 (cc)-(1) aryloxy contenant 6, 10 ou 12 atomes de carbone ;

(dd) aryle contenant 6, 10 ou 12 atomes de carbone et substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyl (2 à 6 atomes de carbone), carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyl, 5-tétrazolo, et acylsulfonamido (c'est-à-dire acylaminosulfonyl et sulfonylaminocarbonyl (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore porter un substituant du groupe fluoro, chloro, bromo, iodo et nitro ;

10 (dd)-(1) aryloxy contenant 6, 10 ou 12 atomes de carbone et substitué sur le carbone par 1 à 3 radicaux choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyl (2 à 6 atomes de carbone), carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyl, 5-tétrazolo, acylsulfonamido (c'est-à-dire acylaminosulfonyl et sulfonylaminocarbonyl) (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore porter un substituant choisi dans le groupe des substituants fluoro, chloro, bromo, iodo et nitro ;

(ee) cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) ;

25 (ee)-(1) cycloalkyloxy contenant 3 à 15 atomes de carbone ;

(ff) un groupe hétérocyclique aliphatique d'au moins 4 atomes de carbone contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant l'azote et l'oxygène (par exemple morpholine, pipérazine), le groupe hétérocyclique aliphatique pouvant facultativement contenir 1 ou 2 doubles liaisons, ce groupe hétérocyclique aliphatique pouvant être substitué au niveau de tout atome d'azote avec un groupe alkyle contenant 1 à 6 atomes de carbone, un groupe alcanoyl contenant 1 à 6 atomes de carbone, un groupe aryloxy-carbonyl dont la partie aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkyloxy-carbonyl dont le groupe aralkyle contient 7 à 13 atomes de carbone ou un groupe alkoxycarbonyl dont le groupe alkyle contient 1 à 6 atomes de carbone ;

30 (ff)-(1) un groupe oxy hétérocyclique aliphatique dont la liaison oxy est attachée directement à un atome de carbone du groupe hétérocyclique aliphatique d'au moins 5 atomes contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes, chacun étant choisi indépendamment dans le groupe comprenant l'azote et l'oxygène (par exemple morpholine, pipérazine), le groupe hétérocyclique aliphatique pouvant facultativement contenir 1 ou 2 doubles liaisons, ce groupe hétérocyclique aliphatique pouvant être substitué au niveau de tout atome d'azote avec un groupe alkyle contenant 1 à 6 atomes de carbone, un groupe alcanoyl contenant 1 à 6 atomes de carbone, un groupe aryloxy-carbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkyloxy-carbonyl dont le groupe aralkyle contient 7 à 13 atomes de carbone ou un groupe alkoxycarbonyl dont le groupe alkyle contient 1 à 6 atomes de carbone ;

35 (gg) un groupe hétérocyclique aromatique contenant (1) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant le soufre, l'azote et l'oxygène et (2) 1 à 3 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et à titre facultatif, dont jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent porter un représentant du groupe comprenant les substituants fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alcanoyl contenant 2 à 6 atomes de carbone, carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone) et aminocarbonyl, et sous réserve en outre que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone ;

50 (gg)-(1) un groupe oxy hétérocyclique aromatique dont la liaison oxy est attachée directement à un atome de carbone d'un groupe hétérocyclique aromatique contenant (1) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant le soufre, l'azote et l'oxygène et (2) 1 à 3 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et à titre facultatif, dans lequel jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent être substitués avec un représentant du groupe comprenant les

substituants fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alcanoyl contenant 2 à 6 atomes de carbone, carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone) et aminocarbonyl, et sous réserve que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone ;

(hh) alkyluréido dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(hh)-(1) cycloalkyluréido dont le groupe alkyle contient 3 à 15 atomes de carbone ;

(ii) aralkyluréido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(jj) aryluréido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(jj)-(1) aryluréido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone et est substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyl (2 à 6 atomes de carbone), carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyl, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyl et sulfonylaminocarbonyl) (1 à 15 atomes de carbone) comprenant un groupe acylsulfonamido dont le groupe acyle contient 1 à 7 atomes de carbone lorsqu'il occupe la portion terminale de l'acylsulfonamide et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, ce radical puisse encore être substitué par un représentant du groupe des substituants fluoro, chloro, bromo, iodo et nitro ;

Pour l'azote :

(a) alkyle ayant 1 à 3 atomes de carbone ;

(b) alcanoyl contenant 2 à 6 atomes de carbone ;

(c) arylcarbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(d) aralcanoyl contenant 8 à 14 atomes de carbone ;

(e) formyle ;

(f) un groupe hétérocyclique aliphatique dont la liaison amino est attachée directement à un atome de carbone d'un groupe hétérocyclique aliphatique défini en (ff) pour les substituants du carbone ;

(g) un groupe hétérocyclique aromatique dont la liaison amino est attachée directement à un atome de carbone du groupe hétérocyclique aromatique défini en (gg) pour les substituants du carbone.

(IV) un groupe aryle contenant 6, 10 ou 12 atomes de carbone ;

(V) un groupe aryle contenant 6, 10 ou 12 atomes de carbone convenablement substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants fluoro, chloro, bromo, iodo, trifluorométhyle, hydroxy, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alkoxycarbonyl contenant 2 à 6 atomes de carbone, carboxy, alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyl et sulfonylaminocarbonyl) contenant 1 à 15 atomes de carbone et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore porter un substituant choisi dans le groupe des substituants fluoro, chloro, bromo, iodo et nitro ;

(VI) un groupe cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) ;

(VI)-(1) un groupe cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) substitué par un représentant du groupe des substituants carboxy et alkoxycarbonyl dont le groupe alkoxy contient 1 à 4 atomes de carbone ;

(VII) un groupe hétérocyclique aliphatique ayant au moins 5 atomes contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant l'azote et l'oxygène (par exemple morpholine, pipérazine) qui peut être substitué au niveau de tout atome d'azote par un substituant choisi entre un groupe alkyle contenant 1 à 6 atomes de carbone, un groupe alcanoyl contenant 1 à 6 atomes de carbone, un groupe aryloxycarbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkoxycarbonyl dont le groupe aralkyle contient 7 à 13 atomes de carbone et un groupe alkoxycarbonyl contenant 2 à 7 atomes de carbone, sous réserve que lorsque A est un groupe OCO ou NHCO, il doit être attaché à un atome de carbone du groupe hétérocyclique aliphatique ;

(VIII) un groupe hétérocyclique aromatique contenant (a) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant le soufre, l'azote et l'oxygène et (b) 1 à 3 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et à titre facultatif, jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent être substitués

au niveau d'un atome de carbone quelconque avec un représentant du groupe des substituants fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alcanoyle contenant 2 à 6 atomes de carbone, carboxy et
 5 pourvu en outre que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone, sous réserve que lorsque A est un groupe OCO ou NHCO, il doit être attaché à un atome de carbone de l'hétérocycle aromatique ;

(IX) un groupe alcényle de 2 à 10 atomes de carbone portant au moins une double liaison ; et

(X) un groupe alcényle de 2 à 10 atomes de carbone ayant au moins une double liaison et substitué par un représentant du groupe des substituants :

10 (a) aryle ayant 6 à 10 atomes de carbone ;

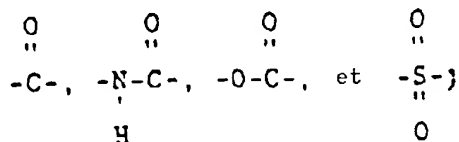
(b) aryle ayant 6 à 10 atomes de carbone substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyle (2 à 6 atomes de carbone), carboxy, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyl et sulfonylaminocarbonyl (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido
 15 contient un radical aryle, le radical aryle puisse encore être substitué par un radical choisi entre fluoro, chloro, bromo, iodo et nitro et

(c) uréidocarbonyl,

R⁴ et R⁶ sont choisis indépendamment entre l'hydrogène et le groupe méthyle ;

20 n a la valeur 0, 1 ou 2 ; et

A est choisi dans le groupe comprenant



30 ou

dans les cas appropriés, les sels d'addition d'acides et de bases de ce composé ; et sous réserve que :

(1) les groupes alkyle puissent être à chaîne droite ou ramifiée ;

35 (2) aucun atome de carbone d'un groupe alkyle ne puisse être directement attaché à deux hétéroatomes ;

(3) aucun hétéroatome ne puisse être attaché directement à un atome de soufre, d'azote ou d'oxygène ; et

40 (4) les groupes alcényle de IX et X pour R³ ne puissent pas être disubstitués en position 1, et qu'un atome de carbone d'une double liaison ne puisse pas être directement attaché à un atome d'oxygène ou d'azote.

2. Composé suivant la revendication 1, dans lequel :

R¹ est un groupe alkyle contenant 3 atomes de carbone ;

45 R² et R⁵ sont choisis chacun, indépendamment, dans le groupe comprenant :

(I) un groupe alkyle contenant 1 à 4 atomes de carbone ;

(II) un groupe alkyle contenant 1 à 4 atomes de carbone, substitué par au moins un représentant du groupe des substituants :

(e) alcanoyl contenant 1 à 3 atomes de carbone ;

50 (f) arylcarbonyl dont le radical aryle contient 6 à 10 atomes de carbone ;

(g) aralcanoyl contenant 8 atomes de carbone ;

(h) amido qui peut être attaché au groupe alkyle par un atome d'azote ou de carbone dudit groupe amido ;

(i) alkylcarbonylamino dont le groupe alkyle contient 1 ou 2 atomes de carbone ;

55 (j) alkylaminocarbonyl dont le groupe alkyle contient 1 ou 2 atomes de carbone ;

(k) arylcarbonylamino dont le groupe aryle contient 6 atomes de carbone ;

(l) aralkylcarbonylamino dont le groupe aralkyle contient 7 atomes de carbone ;

(m) arylaminocarbonyl dont le groupe aryle contient 6 atomes de carbone ;

- (n) aralkylaminocarbonyle dont le groupe aralkyle contient 7 atomes de carbone ;
 (o) carboxy ;
 (p) aryloxy-carbonyle dont le groupe aryle contient 6 atomes de carbone ;
 (q) aralkoxy-carbonyle dont le groupe aralkoxy contient 7 atomes de carbone ;
 5 (r) alcanoyloxy contenant 1 ou 2 atomes de carbone ;
 (s) aroyloxy dont la portion aryle contient 6 atomes de carbone ;
 (t) aralcanoyloxy contenant 8 atomes de carbone ;
 (u) alkylsulfonamido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (v) aralkylsulfonamido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
 10 (w) arylsulfonamido dont le groupe aryle contient 6 ou 10 atomes de carbone ;
 (x) acylsulfonamido contenant 1 à 15 atomes de carbone ;
 (y) alkoxycarbonyle dont le groupe alkoxy contient 1 ou 2 atomes de carbone ;
 (z) aralkoxy-carbonylamino dont le groupe aralkoxy contient 7 atomes de carbone ;
 (aa) aryloxy-carbonylamino dont le groupe aryloxy contient 6 atomes de carbone ;
 15 (bb) alkoxycarbonylamino dont le groupe alkyloxy contient 1 à 3 atomes de carbone ;
 (cc) aryle contenant 6 ou 10 atomes de carbone ;
 (dd) aryle contenant 6 ou 10 atomes de carbone et substitué par 1 à 3 représentants du groupe
 des substituants chloro, bromo, iodo, fluoro, trifluorométhyle, hydroxy, alkyle (1 ou 2 atomes de
 carbone), alkoxy (1 ou 2 atomes de carbone), alkoxycarbonyle (2 ou 3 atomes de carbone),
 20 carboxy, 5-tétrazolo et acylsulfonamido (1 à 15 atomes de carbone) ;
 (ee) cycloalkyle contenant 3 à 15 atomes de carbone ;
 (ff) alkyluréido dont le groupe alkyle contient 1 ou 2 atomes de carbone ;
 (gg) aralkyluréido dont le groupe aralkyle contient 7 atomes de carbone ;
 (hh) aryluréido dont le groupe aryle contient 6 ou 10 atomes de carbone ; et
 25 (III) un groupe aryle de 6 atomes de carbone,
 R³ est choisi dans le groupe comprenant :
 (I) un groupe alkyle contenant 1 à 12 atomes de carbone ;
 (II) un groupe alkyle contenant 1 à 12 atomes de carbone et 1 à 4 hétéroatomes choisis chacun
 indépendamment entre l'azote et d'oxygène ;
 30 (III) un groupe alkyle contenant 1 à 12 atomes de carbone et, à titre facultatif, 1 à 4 hétéroatomes
 choisis chacun indépendamment dans le groupe des atomes d'azote et d'oxygène et substitué sur
 au moins un atome de carbone ou d'azote par 1 à 3 substituants choisis indépendamment dans le
 groupe comprenant :
 Pour le carbone :
 35 (e) alcanoyloxy contenant 1 à 6 atomes de carbone ;
 (f) arylcarbonyle dont le radical aryle contient 6, 10 ou 12 atomes de carbone ;
 (g) aralcanoyloxy contenant 8 à 13 atomes de carbone ;
 (h) amido qui peut être attaché au groupe alkyle par un atome d'azote ou de carbone dudit
 groupe amido ;
 40 (i) alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (j) alkylaminocarbonyle dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (k) arylcarbonylamino dont le groupe aryle contient 6 ou 10 atomes de carbone ;
 (k)-(1) arylcarbonylamino dont le groupe aryle contient 6 ou 10 atomes de carbone et est
 substitué par un représentant du groupe des substituants carboxy, alkoxycarbonyle, dont le
 45 radical alkoxy comprend 1 à 3 atomes de carbone, 5-tétrazolo, et acylsulfonamido contenant 1 à
 15 atomes de carbone ;
 (l) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
 (l)-(1) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone et est
 substitué par un représentant du groupe des substituants carboxy, alkoxycarbonyle dont le radical
 50 alkoxy comprend 1 à 3 atomes de carbone, 5-tétrazolo et acylsulfonamido contenant 1 à 15
 atomes de carbone ;
 (m) arylaminocarbonyle dont le groupe aryle contient 6 ou 10 atomes de carbone ;
 (n) aralkylaminocarbonyle dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
 (o) carboxy ;
 55 (p) aryloxy-carbonyle dont le groupe aryle contient 6 ou 10 atomes de carbone ;
 (q) aralkoxy-carbonyle dont le groupe aralkoxy contient 7 à 13 atomes de carbone ;
 (r) alcanoyloxy contenant 2 ou 3 atomes de carbone ;
 (s) aroyloxy dont la portion aryle contient 6 ou 10 atomes de carbone ;

- (t) aralkanoyloxy contenant 8 à 13 atomes de carbone ;
- (u) alkylsulfonamido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
- (u)-(1) cycloalkylsulfonamido dont la portion cycloalkyle contient 3 à 15 atomes de carbone ;
- (v) aralkylsulfonamido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
- 5 (w) arylsulfonamido dont le groupe aryle contient 6 ou 10 atomes de carbone ;
- (x) acylsulfonamido contenant 1 à 15 atomes de carbone ;
- (y) alkoxycarbonyl dont le groupe alkoxy contient 1 à 3 atomes de carbone ;
- (z) aralkoxycarbonylamino dont le groupe aralkoxy contient 8 à 13 atomes de carbone ;
- (z)-(1) aralkylaminocarbonyloxy dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
- 10 (z)-(2) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (z)-(3) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone et est substitué par un représentant du groupe des substituants aminocarbonyl, aminocarbonylalkyle dont le radical alkyle comprend 1 à 3 atomes de carbone, alkoxycarbonyl ayant 2 à 4 atomes de carbone et carboxy ;
- 15 (aa) aryloxycarbonylamino dont le groupe aryloxy contient 6 ou 10 atomes de carbone ;
- (aa)-(1) arylaminocarbonyloxy dont le groupe aryle contient 6 ou 10 atomes de carbone ;
- (bb) alkoxycarbonylamino dont le groupe alkyloxy contient 1 à 6 atomes de carbone ;
- (bb)-(1) alkoxycarbonylamino dont le groupe alkoxy contient 1 à 6 atomes de carbone et est facultativement lié à un atome de carbone d'un groupe hétérocyclique aromatique comme décrit en (gg) pour R³ ;
- 20 (bb)-(2) alkoxycarbonylamino dont le groupe alkoxy contient 1 à 6 atomes de carbone, substitué par un groupe hétérocyclique aliphatique comme décrit en (ff) pour R³ ;
- (bb)-(3) aryloxyalkylcarbonylamino dont le groupe aryle contient 6 ou 10 atomes de carbone et le groupe alkyle contient 1 à 6 atomes de carbone ;
- 25 (bb)-(4) alkylaminocarbonyloxy dont le groupe alkyle contient 1 à 6 atomes de carbone ;
- (cc) aryle contenant 6 ou 10 atomes de carbone ;
- (cc)-(1) aryloxy contenant 6 ou 10 atomes de carbone ;
- (dd) aryle contenant 6, 10 ou 12 atomes de carbone et portant 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyl (2 à 6 atomes de carbone), carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyl, 5-tétrazolo et acylsulfonamido (1 à 15 atomes de carbone) ;
- 30 (dd)-(1) aryloxy contenant 6, 10 ou 12 atomes de carbone et substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyl (2 à 6 atomes de carbone), carboxy, acylsulfonamido (1 à 15 atomes de carbone), aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyl et 5-tétrazolo ;
- 35 (ee) cycloalkyle contenant 3 à 15 atomes de carbone ;
- (ee)-(1) cycloalkyloxy contenant 3 à 15 atomes de carbone ;
- 40 (ff) un groupe hétérocyclique aliphatique d'au moins 5 atomes contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant l'azote et l'oxygène, le groupe hétérocyclique aliphatique pouvant facultativement contenir 1 ou 2 doubles liaisons, ce groupe hétérocyclique aliphatique pouvant être substitué au niveau de tout atome d'azote avec un groupe alkyle contenant 1 à 6 atomes de carbone, un
- 45 groupe alcanoyl contenant 2 à 6 atomes de carbone, un groupe aryloxycarbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkyloxycarbonyl dont le groupe aralkyle contient 7 à 13 atomes de carbone ou un groupe alkoxycarbonyl dont le groupe alkyle contient 1 à 6 atomes de carbone ;
- (ff)-(1) un groupe oxy hétérocyclique aliphatique dont la liaison oxy est attachée directement à un atome de carbone d'un groupe hétérocyclique aliphatique ayant au moins 5 atomes contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes, chacun étant choisi indépendamment dans le
- 50 groupe des atomes d'azote et d'oxygène, le groupe hétérocyclique aliphatique pouvant facultativement contenir 1 ou 2 doubles liaisons, ce groupe hétérocyclique aliphatique pouvant être substitué au niveau de tout atome d'azote par un groupe alkyle contenant 1 à 6 atomes de
- 55 carbone, un groupe alcanoyl contenant 2 à 6 atomes de carbone, un groupe aryloxycarbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkyloxycarbonyl dont le groupe aralkyle contient 7 à 13 atomes de carbone ou un groupe alkoxycarbonyl dont le
- group alkyle contient 1 à 6 atomes de carbone ;

- (gg) un groupe hétérocyclique aromatique contenant (1) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe des atomes de soufre, d'azote et d'oxygène et (2) 1 à 2 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique et, à titre facultatif, jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent porter un substituant choisi dans le groupe des substituants fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle tel que méthyle, alkoxy contenant 1 ou 2 atomes de carbone, alcanoyl contenant 2 ou 3 atomes de carbone, carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone) et aminocarbonyl et sous réserve en outre que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone ;
- (gg)-(1) un groupe oxy hétérocyclique aromatique dont la liaison oxy est attachée directement à un atome de carbone d'un groupe hétérocyclique aromatique contenant (1) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe des atomes de soufre, d'azote et d'oxygène et (2) 1 ou 2 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et à titre facultatif, jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent être substitués avec un représentant du groupe des substituants fluoro, chloro, bromo, iodo, trifluorométhyle, méthyle, alkoxy contenant 1 ou 2 atomes de carbone, alcanoyl contenant 2 ou 3 atomes de carbone, carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone) et aminocarbonyl, et sous réserve en outre que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone ;
- (hh) alkyluréido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
- (hh)-(1) cycloalkyluréido dont le groupe alkyle contient 3 à 15 atomes de carbone ;
- (ii) aralkyluréido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;
- (jj) aryluréido dont le groupe aryle contient 6 ou 10 atomes de carbone ;
- (jj)-(1) aryléido dont le groupe aryle contient 6 ou 10 atomes de carbone et porte 1 à 3 substituants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxy-carbonyl (2 à 6 atomes de carbone), carboxy, acylsulfonamido (1 à 15 atomes de carbone), aminocarbonylalkyle (2 à 6 atomes de carbone, aminocarbonyl et 5-tétrazolo ;
- Pour l'azote :
- (a) alkyle de 1 à 3 atomes de carbone ;
- (b) alcanoyl contenant 2 à 6 atomes de carbone ;
- (c) arylcarbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
- (d) aralcanoyl contenant 8 à 13 atomes de carbone ;
- (e) formyle ;
- (f) un groupe amino hétérocyclique aliphatique dont la liaison amino est attachée directement à un atome de carbone d'un groupe hétérocyclique aliphatique défini en (ff) pour les substituants du carbone ;
- (g) un groupe hétérocyclique aromatique dont la liaison amino est attachée directement à un atome de carbone du groupe hétérocyclique aromatique défini en (gg) pour les substituants du carbone.
- (IV) un groupe aryle contenant 6 ou 10 atomes de carbone ;
- (V) un groupe aryle contenant 6 ou 10 atomes de carbone convenablement substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alkoxy-carbonyl contenant 2 à 6 atomes de carbone, carboxy, alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone, 5-tétrazolo et acylsulfonamido contenant 1 à 15 atomes de carbone ;
- (VI) un groupe cycloalkyle contenant 3 à 15 atomes de carbone ;
- (VI)-(1) un groupe cycloalkyle contenant 3 à 15 atomes de carbone substitué par un représentant du groupe comprenant le carbone et un radical alkoxy-carbonyl dont le groupe alkoxy contient 1 à 4 atomes de carbone ;
- (VII) un groupe hétérocyclique aliphatique d'au moins 5 atomes contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant l'azote et l'oxygène, qui peut être substitué au niveau de tout atome d'azote par un représentant choisi dans le groupe comprenant le radical méthyle, un groupe alcanoyl contenant 2 à 6 atomes de carbone, un groupe aryloxy-carbonyl dont le groupe aryle contient 6 ou 10 atomes de carbone, un groupe aralkoxy-carbonyl dont le groupe aralkyle contient 7 atomes de carbone et un groupe alkoxy-carbonyl contenant 2 ou 3 atomes de carbone, sous réserve que lorsque A est un groupe

OCO ou NHCO, A doit être attaché à un atome de carbone du groupe hétérocyclique aliphatique ;
 (VIII) un groupe hétérocyclique aromatique contenant (a) 1 à 15 atomes de carbone et 1 à 4
 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant le soufre, l'azote
 et l'oxygène t (b) 1 ou 2 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et
 à titre facultatif, jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent être substitués
 au niveau de tout atome de carbone par un représentant du groupe comprenant les substituants
 fluoro, chloro, bromo, iodo, trifluorométhyle, méthyle, alkoxy contenant 1 ou 2 atomes de carbone,
 alcanyle contenant 2 ou 3 atomes de carbone, carboxy et sous réserve que tout atome d'azote
 puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone, à condition que
 lorsque A représente OCO ou NHCO, A doit être attaché à un atome de carbone de l'hétérocycle
 aromatique ;

(IX) un groupe alcényle de 2 à 10 atomes de carbone portant au moins une double liaison ;

(X) un groupe alcényle de 2 à 10 atomes de carbone ayant au moins une double liaison et un
 substituant choisi dans le groupe des substituants :

(a) aryle de 6 à 10 atomes de carbone ;

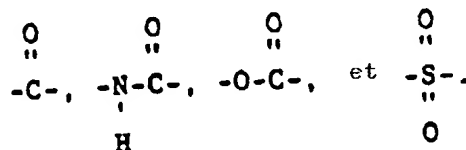
(b) aryle de 6 à 10 atomes de carbone substitué par 1 à 3 substituants choisis indépendamment
 dans le groupe des radicaux chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6
 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alcoxycarbonyle (2 à 6 atomes de
 carbone), carboxy, acylsulfonamido (1 à 15 atomes de carbone) et 5-tétrazolo ; et

(c) uréidocarbonyle ;

R⁴ et R⁶ représentent chacun l'hydrogène ;

n est égal à 1 ; et

A est choisi dans le groupe comprenant



3. Composé suivant la revendication 1, dans lequel

R¹ est un groupe isopropyle ;

R² est choisi dans le groupe comprenant :

(I) un groupe alkyle contenant 2 ou 3 atomes de carbone ;

(II)(q) un groupe éthyle substitué par un radical aralkoxycarbonyle dont le groupe aralkoxy contient 7
 atomes de carbone ;

(w) un groupe butyle substitué par un radical arylsulfonamido dont la portion aryle comprend 6
 atomes de carbone ;

(x) un groupe éthyle substitué par un radical acylsulfonamido contenant 7 atomes de carbone ;

(z) un groupe butyle substitué par un radical aralkyloxycarbonylamino dont la portion aralkoxy
 contient 7 atomes de carbone ;

(cc) un groupe méthyle substitué par un radical aryle contenant 6 atomes de carbone ; et

(III) un groupe aryle contenant 6 atomes de carbone ;

R³ est choisi dans le groupe comprenant :

(I) un groupe alkyle ramifié contenant 4 atomes de carbone ;

(II) un groupe alkyle contenant 5 atomes de carbone et 2 atomes d'oxygène ;

(III)(k) un groupe éthyle substitué par un radical arylcarbonylamino dont la portion aryle contient 6
 atomes de carbone ;

(l) un groupe éthyle substitué par un radical aralkylcarbonylamino dont la portion aralkyle contient
 13 atomes de carbone ;

(n) un groupe éthyle substitué par un radical aralkylaminocarbonyle dont le groupe alkyle contient
 7 atomes de carbone ;

(o) un groupe alkyle contenant 2 ou 10 atomes de carbone et substitué par un radical carboxy ;

(w) un groupe alkyle contenant 5 atomes de carbone et substitué par un radical arylsulfonamido
 dont la portion aryle contient 6 atomes de carbone ;

(x) un groupe éthyle substitué par un radical acylsulfonamido choisi dans le groupe constitué de 2-(méthylsulfonylaminocarbonyl)éthyle, 2-(phénylsulfonylaminocarbonyl)éthyle, 2-[(1-adamantyl)sulfonylaminocarbonyl]éthyle et 2-[(1-naphtyl)sulfonylaminocarbonyl]éthyle ;

5 (y) un groupe alkyle contenant 2 ou 10 atomes de carbone et substitué par un radical méthoxycarbonyle ;

(z) un groupe alkyle contenant 2 à 5 atomes de carbone et substitué par un radical aralkoxycarbonyle dont la portion aralkoxy contient 7 atomes de carbone ;

(aa) un groupe alkyle contenant 5 atomes de carbone et substitué par un radical aryloxy-carbonylamino dont la portion aryloxy contient 6 atomes de carbone ;

10 (bb) un groupe éthyle substitué par un radical alkoxy-carbonylamino dont le groupe alkyle contient 4 atomes de carbone ; et un groupe alkyle contenant 5 atomes de carbone et substitué par un radical alkoxy-carbonylamino dont le groupe alkoxy contient 2 atomes de carbone et est substitué sur l'atome terminal de carbone au moyen d'une liaison directe attachée à un atome de carbone d'un hétérocycle aromatique contenant 5 atomes de carbone et 1 atome d'azote ;

15 (bb)-(3) un groupe propyle substitué par un radical aryloxyalkyl-carbonylamino dont le groupe aryle contient 6 atomes de carbone et le groupe alkyle est un groupe méthyle ;

(cc) un groupe méthyle ou butyle substitué par un radical aryle contenant 6 atomes de carbone ; et un groupe alkyle ramifié contenant 5 atomes de carbone et substitué par deux groupes aryle contenant chacun 6 atomes de carbone ;

20 (dd) un représentant du groupe comprenant un radical alkyle contenant 1 ou 2 atomes de carbone et substitué par un radical aryle contenant 6 atomes de carbone, le radical aryle étant en outre substitué par un radical carboxy ; un groupe méthyle substitué par un radical aryle contenant 6 atomes de carbone, le radical aryle étant en outre substitué par un radical méthoxycarbonyle ; un groupe éthyle substitué par un radical aryle contenant 6 atomes de carbone, le radical aryle étant en outre substitué par un radical éthoxycarbonyle ; et un groupe éthyle substitué par un radical aryle contenant 6 atomes de carbone, le groupe aryle étant en outre substitué par un radical acylsulfonamido contenant 7 atomes de carbone ;

(ee) un groupe éthyle substitué par un radical cycloalkyle contenant 10 atomes de carbone ;

30 (ff) un groupe éthyle substitué par un hétérocycle aliphatique contenant 4 atomes de carbone, 1 atome d'azote et 1 atome d'oxygène ;

(gg) un groupe alkyle contenant 1 ou 2 atomes de carbone et substitué par un hétérocycle aromatique contenant 4 atomes de carbone et 1 atome de soufre ; et un groupe éthyle substitué par un hétérocycle aromatique contenant 5 atomes de carbone et 1 atome d'azote ;

35 (jj)-(1) un groupe alkyle contenant 5 atomes de carbone et substitué par un radical aryluréido dont la portion aryle contient 6 atomes de carbone et dont la portion aryle est en outre substituée par un radical éthoxycarbonyle ou carboxy ;

(zz) un groupe propyle substitué par un radical aryloxy dont la partie aryle contient 6 atomes de carbone ; un groupe alkyle ramifié contenant 5 atomes de carbone et substitué par 2 groupes aryloxy contenant chacun 6 atomes de carbone ;

40 (zzz) un groupe méthyle ou propyle substitué par un radical aryloxy contenant 6 atomes de carbone, dont le radical aryloxy est en outre substitué par un radical aminocarbonyle ; et un groupe méthyle substitué par un radical aryloxy contenant 6 atomes de carbone, dont le radical aryloxy est en outre substitué par un radical éthoxycarbonyle ;

(IV) un groupe aryle contenant 6 ou 10 atomes de carbone ;

45 (V) un groupe aryle contenant 6 atomes de carbone substitué par un représentant du groupe comprenant les substituants fluoro, hydroxy, carboxy, méthoxy, éthoxy, méthoxycarbonyle, éthoxycarbonyle, méthylcarbonylamino, un groupe acylsulfonamido contenant 2 atomes de carbone, un groupe acylsulfonamido contenant 7 atomes de carbone, un groupe acylsulfonamido contenant 11 atomes de carbone, un groupe acylsulfonamido contenant 14 atomes de carbone ; un groupe aryle contenant 6 atomes de carbone et substitué par 2 radicaux chloro ; et un groupe aryle contenant 6 atomes de carbone et substitué par un radical chloro et un radical amino ;

(VI) un groupe cycloalkyle contenant 10 atomes de carbone ;

(VI)-(1) un groupe cycloalkyle contenant 5 atomes de carbone et substitué par un radical carboxy ou éthoxycarbonyle ; et

55 (X) un groupe alcényle contenant 2 atomes de carbone et substitué par un représentant du groupe comprenant les substituants carboxy, carboxyphényle, éthoxycarbonyle, uréidocarbonyle, acylsulfonamido, et 4-carboxyphényle.

R⁴ est l'hydrogène ;

R⁵ est choisi dans le groupe comprenant :

- (I) un radical n-butyle ;
- (II)(q) un groupe éthyle substitué par un radical aralkoxycarbonyl dont le groupe aralkoxy contient 7 atomes de carbone ; et
- 5 (II)(z) un groupe butyle substitué par un radical aralkyloxycarbonylamino dont le groupe aralkyle contient 7 atomes de carbone ;

A est tel que défini ci-dessus ; et
n est égal à 1.

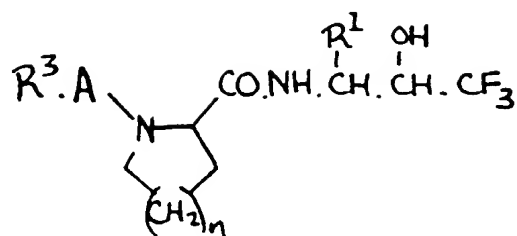
10 4. Composé suivant la revendication 1, choisi dans le groupe comprenant :

- 1) le 3S(ou R)-phénylméthoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 2) le 3(RS)-[(phénylméthoxy)carbonyl]-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 15 3) le 3(RS)-[(4-éthoxycarbonyl)phényl]aminocarbonyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 4) le 3(RS)-[(4-carboxyphényl)aminocarbonyl]-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 5) le 3(RS)-[(4-phénylbutyl)carbonyl]-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 20 6) le 3(RS)-2-[2-(tricyclo[3,3,1,1^{3,7}]déc-1-yl)-éthoxycarbonyl]-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 7) le 3(RS)-[(4-méthoxyphényl)carbonyl]-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 25 8) le 3(RS)-N²,N⁶-di[(phénylméthoxy)carbonyl]-L-lysyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 9) le 3(RS)-[(phénylméthoxy)carbonyl]-L-phénylalanyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 10) le 3(RS)-[2-(méthoxycarbonyl)éthyl]carbonyl-L-norleucyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 30 11) le 3(RS)-[2-(2-carboxyéthyl)carbonyl]-L-norleucyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 12) l'ester phénylméthyle de 3(RS)-[(phénylméthoxy)carbonyl]-L-alpha-glutamyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 35 13) le 3(RS)-N²-[2-(méthoxycarbonyl)éthyl]carbonyl-L-N⁶-[(phénylméthoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 14) le 3(RS)-N²-[(2-carboxyéthyl)carbonyl]-N⁶-[(phénylméthoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 15) le 3S(ou R)-N²,N⁶-di[(phénylméthoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 40 16) le 3(RS)-(1-naphtyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 17) le 3(RS)-[4-(méthylsulfonylaminocarbonyl)phényl]aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 18) le 3(RS)-[2-(4-morpholiny)éthoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 45 19) le 3(RS)-[(2,4-dichlorophényl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 20) le 3(RS)-phénoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 21) le 3(RS)-[2-(2-pyridyl)éthoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 50 22) le 3(RS)-[4-(phénylsulfonylaminocarbonyl)phényl]aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 23) le 3(RS)-[2-(3-thiophényl)éthoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 55 24) le 3(RS)-(phénylméthoxycarbonyl)-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 25) le 3(RS)-(phénoxycarbonyl)-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;

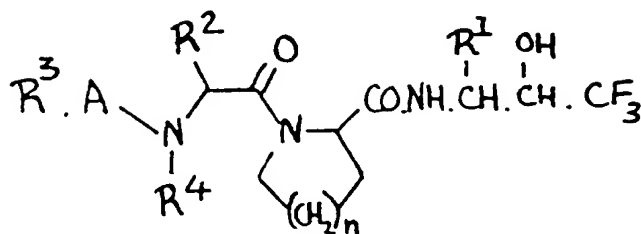
- 26) le 3(RS)-N²-(1,1-diméthyléthoxycarbonyl)-N⁶-phénylméthoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 27) le 3(RS)-[2-(tricyclo[3,3,1,1^{3,7}]-déc-1-yl)éthoxycarbonyl]-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 5 28) le 3(RS)-(4-hydroxycarbonylphényl)aminocarbonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 29) le 3(RS)-N⁶-phénylméthoxycarbonyl-N²-phénylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 30) le 3(RS)-[Z-(4-aminocarbonylamino-1,4-dioxo-2-butényl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 10 31) le 3(RS)-phénylaminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 32) le 3(RS)-[4-[(1-naphtylsulfonyl)aminocarbonyl]phényl]aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 33) le 3(RS)-N²-(4-hydroxycarbonylphényl)aminocarbonyl-N⁶-phénylméthoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 15 34) le 3(RS)-(4-hydroxycarbonylphényl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 35) le 3(RS)-(tricyclo[3.3.1.1^{3,7}]-déc-1-yl)sulfonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 20 36) le 3(RS)-(4-méthoxycarbonylphényl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 37) le 3(RS)-(4-hydroxycarbonylphényl)aminocarbonyl-L-phénylalani-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 38) le 3(RS)-(4-méthoxycarbonylphényl)méthoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 25 39) le 3(RS)-[E-3-(4-éthoxycarbonylphényl)-1-oxoprop-2-ényl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 40) le 3(RS)-(2-éthoxycarbonylphényl)aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 30 41) le 3(RS)-4-[(4-nitrophényl)sulfonylaminocarbonyl]phénylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 42) l'ester phénylméthylque de 3(RS)-phénylméthoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 35 43) le 3S(ouR)-(tricyclo[3.3.1.1^{3,7}]-déc-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 44) le 3(RS)-phénylméthoxycarbonyl-L-[5-(phénylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 45) le 3(RS)-[4-(phénylsulfonylaminocarbonyl)phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 40 46) le 3(RS)-[4-[(4-bromophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 47) le 3(RS)-4-(1-naphtylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 48) le 3(RS)-[2-(4-aminocarbonylphénoxy)-1-oxoéthyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 45 49) le 3(RS)-(4-hydroxycarbonylphényl)méthoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 50) le 3(RS)-[4-(4-(2-amino-2-oxoéthyl)phénoxy)-1-oxobutyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 50 51) le 3(RS)-E-[3-(4-hydroxycarbonylphényl)-1-oxoprop-2-ényl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 52) le 3(RS)-[2-(4-éthoxycarbonylphénoxy)-1-oxoéthyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 53) le 3(RS)-[3-(4-éthoxycarbonylphényl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 55 54) le 3(RS)-4-hydroxybenzoyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 55) le 3(RS)-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;

- 56) le 3(RS)-[3-(4-hydroxycarbonylphényl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 57) le 3(RS)-[3-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phényl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 58) le 3(RS)-E-[3-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phényl]-1-oxoprop-2-ényl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 59) le 3(RS)-[1-[4-[(4-bromophényl)sulfonyl]phénylméthyl]aminocarbonyl]phényl]-1-oxométhyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 60) le 3R(ou S)-(tricyclo[3.3.1.1^{3,7}]déc-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 61) le 3S(ou R)-[4-(phénylsulfonylaminocarbonyl)phénylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 62) le 3S(ou R)-phénylméthoxycarbonyl-L-phénylglycyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 63) le 3S(ou R)-[4-[(4-bromophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 64) le 3S(ou R)-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 65) le 3S(ou R)-phénylméthoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 66) le 3S(ou R)-[(4-carboxyphényl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 67) le 3(RS)-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 68) le 3(RS)-N²,N⁶-di(phénylméthoxycarbonyl)-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 69) le 3(RS)-[1,4-dioxo-4-(phénylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 70) le 3(RS)-[4-(méthylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 71) le 3(RS)-N²-[1,4-dioxo-4-(phénylsulfonylamino)butyl]-N⁶-phénylméthoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ; et
- 72) le 3(RS)-[1,4-dioxo-4-[(tricyclo[3.3.1.1^{3,7}]déc-1-yl)sulfonylamino]butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide.
5. Composé suivant la revendication 4, choisi dans le groupe des composés suivants :
- 1) 3(RS)-[(4-carboxyphényl)aminocarbonyl]-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 2) le 3(RS)-[(2-carboxyéthyl)carbonyl]-L-norleucyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 3) le 3(RS)-N²-[(2-carboxyéthyl)carbonyl]-N⁶-[(phénylméthoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-méthyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide ;
- 4) 3(RS)-[4-(méthylsulfonylaminocarbonyl)phénylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 5) 3(RS)-[4-(phénylsulfonylaminocarbonyl)phénylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 6) 3(RS)-(4-hydroxycarbonylphényl)aminocarbonyl-L-α-aminobutyryl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 7) 3(RS)-[2-(4-aminocarbonylamino-1,4-dioxo-2-butényl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 8) 3(RS)-[[4-[(1-naphtylsulfonyl)aminocarbonyl]phényl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 9) 3(RS)-N²-(4-hydroxycarbonylphényl)aminocarbonyl-N⁶-phénylméthoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 10) 3(RS)-(4-hydroxycarbonylphényl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 11) 3(RS)-(4-hydroxycarbonylphényl)aminocarbonyl-L-phénylalanyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;

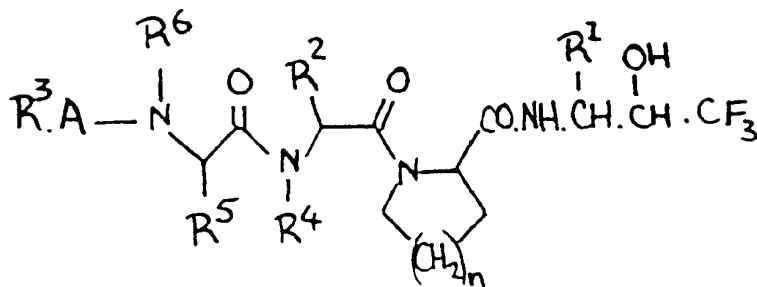
- 12) 3(RS)-4-[(4-nitrophényl)sulfonylaminocarbonyl]phénylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 13) 3(RS)-phénylméthoxycarbonyl-L-[5-(phénylsulfonylamino)glutanyl]-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 5 14) 3(RS)-[4-phénylsulfonylaminocarbonyl]phénylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 15) 3(RS)-[4-[(4-bromophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 16) 3(RS)-4-(1-naphtylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 17) 3(RS)-(4-hydroxycarbonylphényl)méthoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 18) 3(RS)-E-[3-(4-hydroxycarbonylphényl)-1-oxoprop-2-ényl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 19) 3(RS)-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 20) 3(RS)-[3-(4-hydroxycarbonylphényl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 21) 3(RS)-[3-4-[(4-chlorophényl)sulfonylaminocarbonyl]phényl]-1-oxopropyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 22) 3(RS)-E-[3-4-[(4-chlorophényl)sulfonylaminocarbonyl]phényl]-1-oxoprop-2-ényl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 23) 32(ou R)-[4-(phénylsulfonylaminocarbonyl)phénylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 24) 32(ou R)-[4-[(4-bromophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 25) 3S(ou R)-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 26) 3S(ou R)-[4-(carboxyphényl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 27) 3(RS)-[1,4-dioxo-4-(phénylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 28) 3(RS)-[4-(méthylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ; et
- 29) 3(RS)-N²-[1,4-dioxo-4-(phénylsulfonylamino)butyl]-N⁶-phénylméthoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide.
6. Composé suivant la revendication 5, choisi dans le groupe comprenant :
- 1) le 3(RS)-[4-[(1-naphtylsulfonyl)aminocarbonyl]phényl]aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 2) le 3(RS)-[4-[(4-bromophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 3) le 3(RS)-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide ;
- 4) le 3S(ou R)-[4-[(4-bromophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide et
- 5) le 3S(ou R)-[4-[(4-chlorophényl)sulfonylaminocarbonyl]phénylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-méthyl-2-oxopentyl)]-L-prolinamide.
7. Composé suivant la revendication 1, dans lequel ledit sel d'addition d'acide est un sel formé avec l'acide chlorhydrique, bromhydrique, sulfurique, nitrique, citrique, maléique, fumarique ou acétique.
8. Composé suivant la revendication 1, dans lequel le sel d'addition de base est un sel formé avec un hydroxyde de métal alcalin, un carbonate de métal alcalin, un bicarbonate de métal alcalin, un hydroxyde de métal alcalino-terreux ou un sel d'amine organique.
9. Procédé de production des composés suivant l'une quelconque des revendications 1 à 8, qui consiste à oxyder un composé de formule VIIa, VIIb ou VIIc



VIIa



VIIb



VIIc

pour former un premier composé de formule Ia, Ib ou Ic.

10. Procédé suivant la revendication 9, qui consiste à effectuer une oxydation en utilisant un représentant du groupe comprenant les suivants :

- (a) chlorure d'oxalyle, diméthylsulfoxyde et une amine tertiaire dans le chlorure de méthylène ;
- (b) anhydride acétique et diméthylsulfoxyde ;
- (c) complexe de trioxyde de chrome et de pyridine dans du chlorure de méthylène ; et
- (d) periodinane de Dess-Martin dans le chlorure de méthylène.

11. Procédé suivant la revendication 10, dans lequel ladite oxydation consiste à utiliser le periodinane de Dess-Martin dans du chlorure de méthylène.

12. Procédé suivant la revendication 9, qui consiste en outre à former un second composé de formule Ia, Ib ou Ic contenant un groupe carboxy dans R², R³ ou R⁵ à partir dudit premier composé de formule Ia, Ib ou respectivement Ic, le premier composé contenant un groupe ester d'acide carboxylique dans R², R³ ou R⁵, ledit procédé consistant à convertir ledit groupe ester d'acide carboxylique en le groupe carboxy correspondant.

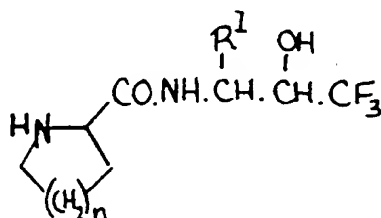
13. Procédé suivant la revendication 12, qui consiste à convertir ledit groupe ester d'acide carboxylique en le groupe carboxy correspondant par hydrolyse.

14. Procédé suivant la revendication 9 ou la revendication 12, qui consiste en outre à former un troisième composé de formule Ia, Ib ou Ic contenant un groupe sulfonylaminocarbonyl dans R², R³ ou R⁵ à

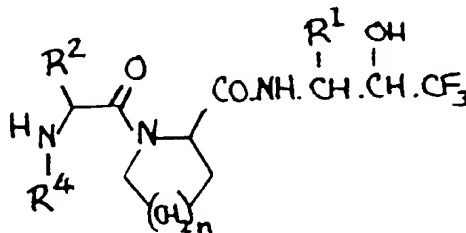
partir du premier ou du second composé de formule respective Ia, Ib ou Ic, le premier ou le second composé contenant un groupe carboxy dans R², R³ ou R⁵, par couplage dudit groupe carboxy avec un groupe amino d'un sulfonamide.

- 5 15. Procédé suivant la revendication 14, qui comprend une opération de couplage effectuée au choix en utilisant un représentant du groupe comprenant :
- (a) le chlorhydrate de 1-éthyl-3-(3-diméthylaminopropyl)carbodiimide et la 4-diméthylaminopyridine dans le chlorure de méthylène ; et
- (b) le 1,3-dicyclohexylcarbodiimide et la 4-diméthylaminopyridine dans le chlorure de méthylène.
- 10 16. Composition pharmaceutique comprenant un composé suivant la revendication 1 ou un sel de ce composé en association avec un diluant ou support non toxique acceptable du point de vue pharmaceutique.
- 15 17. Composé de formule IVa, IVb ou IVc :

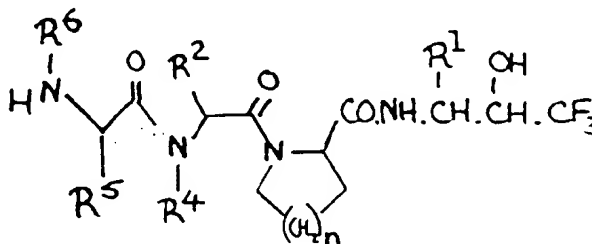
IVa



IVb



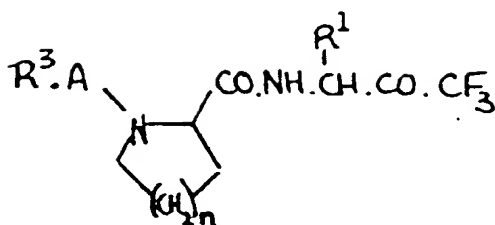
IVc



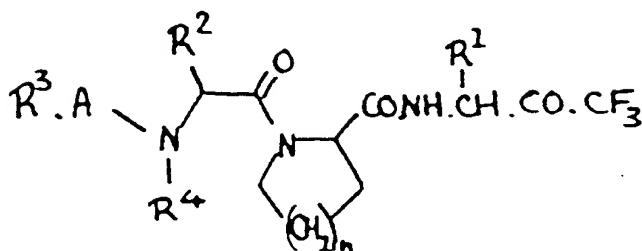
dans laquelle R¹, R², R⁴, R⁵, R⁶ et n ont l'une quelconque des définitions données dans la revendication 1.

Revendications pour l'Etat contractant suivant : AT

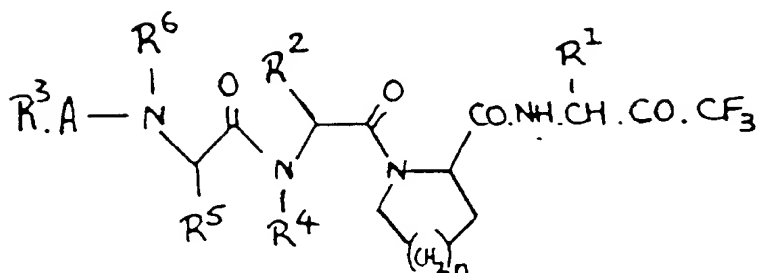
1. Procédé de production d'un composé de formule Ia, Ib ou Ic



Ia



Ib



Ic

dans laquelle

R¹ est un groupe alkyle contenant 1 à 5 atomes de carbone et de préférence 2 à 5 atomes de carbone ;

R² et R⁵ sont choisis chacun, indépendamment, dans le groupe comprenant :

(I) un groupe alkyle contenant 1 à 10 atomes de carbone ;

(II) un groupe alkyle contenant 1 à 6 atomes de carbone, substitué par au moins un représentant du groupe des substituants suivants :

(a) hydroxy ;

(b) amino ;

(c) alkylamino contenant 1 à 6 atomes de carbone ;

(d) dialkylamino contenant dans chaque groupe alkyle 1 à 6 atomes de carbone ;

(e) alcanoyloxy contenant 1 à 6 atomes de carbone ;

(f) arylcarbonyloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(g) aralcanoyloxy contenant 8 à 13 atomes de carbone ;

(h) amido qui peut être attaché au groupe alkyle par un atome d'azote ou de carbone dudit groupe amido ;

(i) alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(j) alkylaminocarbonyloxy dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(k) arylcarbonylamino dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(l) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(m) arylaminocarbonyloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(n) aralkylaminocarbonyloxy dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(o) carboxy ;

(p) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(q) aralkoxy dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(r) alcanoyloxy contenant 1 à 6 atomes de carbone ;

(s) aryloxy dont la portion aryle contient 6, 10 ou 12 atomes de carbone ;

- (t) aralcanoyloxy contenant 8 à 14 atomes de carbone ;
 (u) alkylsulfonamido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (v) aralkylsulfonamido dont le groupe aralkyl contient 7 à 13 atomes de carbone ;
 (w) arylsulfonamido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 5 (x) acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylaminocarbonyle) comprenant un groupe acylsulfonamido dont le groupe acyle contient 1 à 7 atomes de carbone lorsqu'il constitue la portion terminale de l'acylsulfonamide et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse en outre être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;
 10 (y) alkoxy-carbonyle dont le groupe alkoxy contient 1 à 6 atomes de carbone ;
 (z) aralkoxy-carbonylamino dont le groupe aralkoxy contient 8 à 13 atomes de carbone (par exemple benzyloxy-carbonylamino) ;
 (aa) aryloxy-carbonylamino dont le groupe aryloxy contient 6, 10 ou 12 atomes de carbone ;
 (bb) alkoxy-carbonylamino dont le groupe alkyloxy contient 1 à 6 atomes de carbone ;
 15 (cc) aryle contenant 6, 10 ou 12 atomes de carbone (par exemple phényle, biphenyle, naphtyle) ;
 (dd) aryle contenant 6, 10 ou 12 atomes de carbone et substitué par 1 à 3 représentants du groupe comprenant les substituants chloro, bromo, iodo, fluoro, trifluorométhyle, hydroxy, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxy-carbonyle (1 à 6 atomes de carbone), carboxy, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylaminocarbonyle (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido
 20 contient un radical aryle, ce dernier puisse encore être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;
 (ee) cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) ;
 25 (ff) alkyluréido dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (gg) aralkyluréido dont le groupe aralkyle contient 8 à 13 atomes de carbone ;
 (hh) aryluréido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ; et
 (III) un groupe aryle de 6 atomes de carbone, par exemple phényle,
 R³ est choisi dans le groupe comprenant :
 30 (I) un groupe alkyle contenant 1 à 12 atomes de carbone ;
 (II) un groupe alkyle contenant 1 à 12 atomes de carbone et 1 à 4 hétéroatomes choisis chacun indépendamment entre l'azote et l'oxygène ;
 (III) un groupe alkyle contenant 1 à 12 atomes de carbone et, à titre facultatif, 1 à 4 hétéroatomes choisis chacun indépendamment entre l'azote et l'oxygène, et substitué sur au moins l'un des
 35 atomes de carbone et d'azote par 1 à 3 substituants choisis indépendamment dans le groupe des substituants suivants :
 Pour le carbone :
 (a) hydroxy, sous réserve qu'il ne puisse pas se trouver sur un atome de carbone directement lié à A ;
 40 (b) amino, sous réserve qu'il ne puisse pas se trouver sur un atome de carbone directement lié à A ;
 (c) alkylamino contenant 1 à 6 atomes de carbone, sous réserve qu'il ne puisse pas se trouver sur un atome de carbone directement lié à A ;
 (d) dialkylamino dont chaque groupe alkyle contient 1 à 6 atomes de carbone, sous réserve qu'il
 45 ne puisse pas se trouver sur un atome de carbone directement lié à A ;
 (e) alcanoyloxy contenant 1 à 6 atomes de carbone ;
 (f) arylcarbonyle dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 (g) aralcanoyloxy contenant 8 à 13 atomes de carbone ;
 (h) amido qui peut être attaché au groupe alkyle par un atome d'azote ou de carbone dudit
 50 groupe amido ;
 (i) alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (j) alkylaminocarbonyle dont le groupe alkyle contient 1 à 6 atomes de carbone ;
 (k) arylcarbonylamino dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;
 55 (k)-(1) arylcarbonylamino dont le groupe aryle contient 6, 10 ou 12 atomes de carbone et porte un substituant choisi entre carboxy, alkoxy-carbonyle, dont le radical alkoxy comprend 1 à 3 atomes de carbone, 5-tétrazolo, et acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylaminocarbonyle) contenant 1 à 15 atomes de carbone et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse être encore substitué par un substituant

choisi entre fluoro, chloro, bromo, iodo et nitro ;

(l) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(l)-(1) aralkylcarbonylamino dont le groupe aralkyle contient 7 à 13 atomes de carbone et est substitué par un substituant choisi entre carboxy, alkoxycarbonyle dont le radical alkoxy contient 1 à 3 atomes de carbone, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylamino-carbonyle) contenant 1 à 15 atomes de carbone et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;

(m) arylaminocarbonyle dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(n) aralkylaminocarbonyle dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(o) carboxy ;

(p) aryloxy-carbonyle dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(q) aralkoxy-carbonyle dont le groupe aralkoxy contient 7 à 13 atomes de carbone ;

(r) alcanoyloxy contenant 1 à 6 atomes de carbone ;

(s) aroyloxy dont le portion aryle contient 6, 10 ou 12 atomes de carbone ;

(t) aralcanoyloxy contenant 8 à 13 atomes de carbone ;

(u) alkylsulfonamido dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(u)-(1) cycloalkylsulfonamido dont la portion cycloalkyle contient 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) ;

(v) aralkylsulfonamido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(w) arylsulfonamido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(x) acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylamino-carbonyle) (1 à 15 atomes de carbone) comprenant un groupe acylsulfonamido dont le groupe acyle contient 1 à 7 atomes de carbone lorsqu'il occupe la position terminale de l'acylsulfonamide, et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;

(y) alkoxycarbonyle dont le groupe alkoxy contient 1 à 6 atomes de carbone ;

(z) aralkoxy-carbonylamino dont le groupe aralkoxy contient 8 à 13 atomes de carbone (par exemple benzyloxy-carbonylamino) ;

(z)-(1) aralkylaminocarbonyloxy dont le groupe aralkyle contient 8 à 13 atomes de carbone ;

(z)-(2) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(z)-(3) aryloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone et est substitué par un représentant choisi entre aminocarbonyle, aminocarbonylalkyle dont le radical alkyle contient 1 à 3 atomes de carbone, alkoxycarbonyle ayant 1 à 3 atomes de carbone et carboxy ;

(aa) aryloxy-carbonylamino dont le groupe aryloxy contient 6, 10 ou 12 atomes de carbone ;

(aa)-(1) arylaminocarbonyloxy dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(bb) alkoxycarbonylamino dont le groupe alkyloxy contient 1 à 6 atomes de carbone ;

(bb)-(1) alkoxycarbonylamino dont le groupe alkoxy contient 1 à 6 atomes de carbone et est facultativement lié par du carbone à un atome de carbone d'un groupe hétérocyclique aromatique comme indiqué en (gg) pour R³ ;

(bb)-(2) alkoxycarbonylamino dont le groupe alkoxy contient 1 à 6 atomes de carbone, substitué par un groupe hétérocyclique aliphatique comme décrit en (ff) pour R³ ;

(bb)-(3) aryloxyalkylcarbonylamino dont le groupe aryle contient 6 ou 10 atomes de carbone et le groupe alkyle comprend 1 à 6 atomes de carbone ;

(bb)-(4) alkylaminocarbonyloxy dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(cc) aryle contenant 6, 10 ou 12 atomes de carbone (par exemple phényle, naphtyle, biphényle) ;

(cc)-(1) aryloxy contenant 6, 10 ou 12 atomes de carbone ;

(dd) aryle contenant 6, 10 ou 12 atomes de carbone et substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyle (2 à 6 atomes de carbone), carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyle, 5-tétrazolo, et acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylamino-carbonyle) (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;

(dd)-(1) aryloxy contenant 6, 10 ou 12 atomes de carbone et substitué sur le carbone par 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de

carbone), alkoxy-carbonyl (2 à 6 atomes de carbone), carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyl, 5-tétrazolo, acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylaminocarbonyl) (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;

(ee) cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) ;

(ee)-(1) cycloalkyloxy contenant 3 à 15 atomes de carbone ;

(ff) un groupe hétérocyclique aliphatique d'au moins 4 atomes de carbone contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant l'azote et l'oxygène (par exemple morpholine, pipérazine), le groupe hétérocyclique aliphatique pouvant facultativement contenir 1 ou 2 doubles liaisons, ce groupe hétérocyclique aliphatique pouvant être substitué au niveau de tout atome d'azote avec un groupe alkyle contenant 1 à 6 atomes de carbone, un groupe alcanoyl contenant 1 à 6 atomes de carbone, un groupe aryloxy-carbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkyloxy-carbonyl dont le groupe aralkyle contient 7 à 13 atomes de carbone ou un groupe alkoxy-carbonyl dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(ff)-(1) un groupe oxy hétérocyclique aliphatique dont la liaison oxy est attachée directement à un atome de carbone du groupe hétérocyclique aliphatique d'au moins 5 atomes contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes, chacun étant choisi indépendamment dans le groupe comprenant l'azote et l'oxygène (par exemple morpholine, pipérazine), le groupe hétérocyclique aliphatique pouvant facultativement contenir 1 ou 2 doubles liaisons, ce groupe hétérocyclique aliphatique pouvant être substitué au niveau de tout atome d'azote avec un groupe alkyle contenant 1 à 6 atomes de carbone, un groupe alcanoyl contenant 1 à 6 atomes de carbone, un groupe aryloxy-carbonyl dont le groupe aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkyloxy-carbonyl dont le groupe aralkyle contient 7 à 13 atomes de carbone ou un groupe alkoxy-carbonyl dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(gg) un groupe hétérocyclique aromatique contenant (1) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe des atomes de soufre, d'azote et d'oxygène et (2) 1 à 3 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et à titre facultatif, jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent être substitués avec un substituant choisi entre fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alcanoyl contenant 2 à 6 atomes de carbone, carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone) et aminocarbonyl et pourvu en outre que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone ;

(gg)-(1) un groupe oxy hétérocyclique aromatique dont la liaison oxy est attachée directement à un atome de carbone d'un groupe hétérocyclique aromatique contenant (1) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant le soufre, l'azote et l'oxygène et (2) 1 à 3 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et à titre facultatif, jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent être substitués par un substituant choisi entre fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alcanoyl contenant 2 à 6 atomes de carbone, carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone) et aminocarbonyl, et sous réserve en outre que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone ;

(hh) alkyluréido dont le groupe alkyle contient 1 à 6 atomes de carbone ;

(hh)-(1) cycloalkyluréido dont le groupe alkyle contient 3 à 15 atomes de carbone ;

(ii) aralkyluréido dont le groupe aralkyle contient 7 à 13 atomes de carbone ;

(jj) aryluréido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone ;

(jj)-(1) aryluréido dont le groupe aryle contient 6, 10 ou 12 atomes de carbone et est substitué par 1 à 3 substituants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxy-carbonyl (2 à 6 atomes de carbone), carboxy, aminocarbonylalkyle (2 à 6 atomes de carbone), aminocarbonyl, 5-tétrazolo et acide sulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylaminocarbonyl) (1 à 15 atomes de carbone) comprenant un groupe acylsulfonamido dont le groupe acyle contient 1 à 7 atomes de carbone lorsqu'il occupe la portion terminale de l'acylsulfonamide et sous réserve que lorsque le groupe acylsulfonamido contient un

radical aryle, ce radical puisse encore être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;

Pour l'azote :

- (a) alkyle ayant 1 à 3 atomes de carbone ;
- (b) alcanoye contenant 2 à 6 atomes de carbone ;
- (c) arylcarbonyle dont le radical aryle contient 6, 10 ou 12 atomes de carbone ;
- (d) aralcanoye contenant 8 à 14 atomes de carbone ;
- (e) formyle ;
- (f) un groupe hétérocyclique aliphatique dont la liaison amino est attachée directement à un atome de carbone d'un groupe hétérocyclique aliphatique défini en (ff) pour les substituants du carbone ;
- (g) un groupe hétérocyclique aromatique dont la liaison amino est attachée directement à un atome de carbone du groupe hétérocyclique aromatique défini en (gg) pour les substituants du carbone.
- (IV) un groupe aryle contenant 6, 10 ou 12 atomes de carbone ;
- (V) un groupe aryle contenant 6, 10 ou 12 atomes de carbone convenablement substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants fluoro, chloro, bromo, iodo, trifluorométhyle, hydroxy, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alkoxycarbonyle contenant 2 à 6 atomes de carbone, carboxy, alkylcarbonylamino dont le groupe alkyle contient 1 à 6 atomes de carbone, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylaminocarbonyle) contenant 1 à 15 atomes de carbone et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore être substitué par un substituant choisi entre fluoro, chloro, bromo, iodo et nitro ;
- (VI) un groupe cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle) ;
- (VI)-(1) un groupe cycloalkyle contenant 3 à 15 atomes de carbone (par exemple cyclohexyle, adamantyle, norbornyle), substitué par un représentant du groupe des substituants carboxy et alkoxycarbonyle dont le groupe alkoxy contient 1 à 4 atomes de carbone ;
- (VII) un groupe hétérocyclique aliphatique ayant au moins 5 atomes contenant 1 à 5 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant l'azote et l'oxygène (par exemple morpholine, pipérazine) qui peut être substitué au niveau de tout atome d'azote par un substituant choisi entre un groupe alkyle contenant 1 à 6 atomes de carbone, un groupe alcanoye contenant 1 à 6 atomes de carbone, un groupe aryloxycarbonyle dont le groupe aryle contient 6, 10 ou 12 atomes de carbone, un groupe aralkoxycarbonyle dont le groupe aralkyle contient 7 à 13 atomes de carbone et un groupe alkoxycarbonyle contenant 2 à 7 atomes de carbone, sous réserve que lorsque A représente OCO ou NHCO, il doit être attaché à un atome de carbone du groupe hétérocyclique aliphatique ;
- (VIII) un groupe hétérocyclique aromatique contenant (a) 1 à 15 atomes de carbone et 1 à 4 hétéroatomes dont chacun est choisi indépendamment dans le groupe comprenant le soufre, l'azote et l'oxygène et (b) 1 à 3 noyaux pentagonaux ou hexagonaux dont l'un au moins est aromatique, et à titre facultatif, jusqu'à 3 atomes de carbone du ou des noyaux aromatiques peuvent être substitués au niveau d'un atome de carbone quelconque avec un représentant du groupe comprenant les substituants fluoro, chloro, bromo, iodo, trifluorométhyle, alkyle contenant 1 à 6 atomes de carbone, alkoxy contenant 1 à 6 atomes de carbone, alcanoye contenant 2 à 6 atomes de carbone, carboxy et sous réserve en outre que tout atome d'azote puisse être substitué par un groupe alkyle contenant 1 à 6 atomes de carbone, sous réserve que lorsque A représente OCO ou NHCO, il doit être attaché à un atome de carbone de l'hétérocycle aromatique ;
- (IX) un groupe alcényle de 2 à 10 atomes de carbone portant au moins une double liaison ; et
- (X) un groupe alcényle de 2 à 10 atomes de carbone ayant au moins une double liaison et substitué par un représentant du groupe des substituants :
 - (a) un groupe aryle de 6 ou 10 atomes de carbone ;
 - (b) un groupe aryle de 6 ou 10 atomes de carbone substitué par 1 à 3 représentants choisis indépendamment dans le groupe des substituants chloro, bromo, iodo, fluoro, hydroxy, trifluorométhyle, alkyle (1 à 6 atomes de carbone), alkoxy (1 à 6 atomes de carbone), alkoxycarbonyle (2 à 6 atomes de carbone), carboxy, 5-tétrazolo et acylsulfonamido (c'est-à-dire acylaminosulfonyle et sulfonylaminocarbonyle (1 à 15 atomes de carbone) et sous réserve que lorsque le groupe acylsulfonamido contient un radical aryle, le radical aryle puisse encore être substitué par un représentant du groupe des substituants fluoro, chloro, bromo, iodo et nitro ; et

(c) uréidocarbonyle,

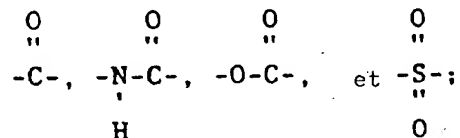
R^4 et R^5 sont choisis indépendamment entre l'hydrogène et un groupe méthyle ;

n a la valeur 0, 1 ou 2 ; et

A est choisi dans le groupe comprenant

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et dans les cas appropriés, les sels d'addition d'acides et de bases de ce composé ; et sous réserve que :

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(1) les groupes alkyle puissent être à chaîne droite ou ramifiée ;

(2) aucun atome de carbone d'un groupe alkyle ne puisse être directement attaché à deux hétéroatomes ;

(3) aucun hétéroatome ne puisse être attaché directement à un atome de soufre, d'azote ou d'oxygène ; et

(4) les groupes alcényle de IX et X pour R^3 ne puissent pas être disubstitués en position 1, et qu'un atome de carbone d'une double liaison ne puisse pas être directement attaché à un atome d'oxygène ou d'azote,

ledit procédé consistant à oxyder un composé de formule respective VIIa, VIIb ou VIIc,

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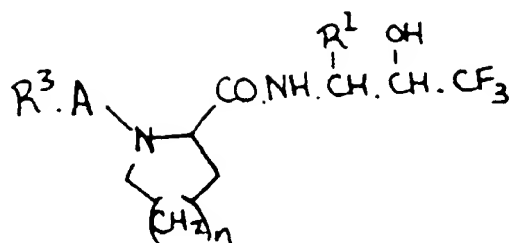
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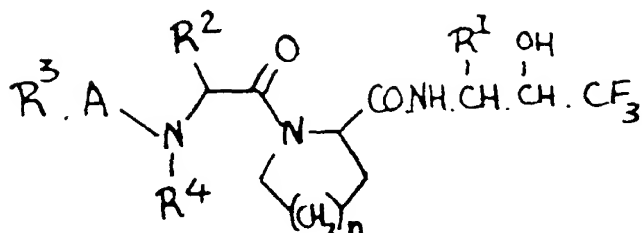
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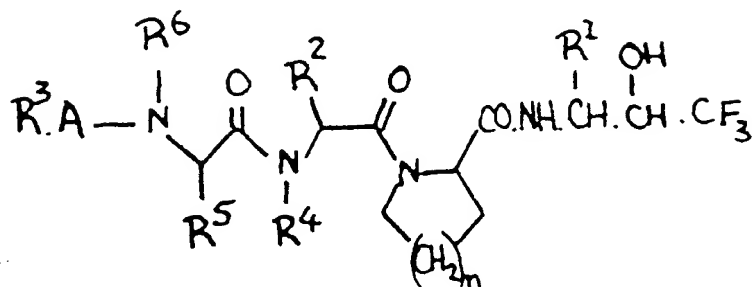
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VIIa



VIIb



VIIc

2. Procédé suivant la revendication 1, qui comprend une oxydation choisie dans un groupe constitué comme suit :
 - (a) chlorure d'oxalyle, diméthylsulfoxyde et une amine tertiaire dans le chlorure de méthylène ;
 - (b) anhydride acétique et diméthylsulfoxyde ;
 - (c) complexe de trioxyde de chrome et de pyridine dans le chlorure de méthylène ; et
 - (d) periodinane de Dess-Martin dans le chlorure de méthylène.
3. Procédé suivant la revendication 1 ou la revendication 2, dans lequel ladite oxydation consiste à utiliser le periodinane de Dess-Martin dans le chlorure de méthylène.
4. Procédé suivant la revendication 1, consistant en outre à former un second composé de formule Ia, Ib ou Ic contenant un groupe carboxy dans R², R³ ou R⁵ à partir dudit premier composé de formule respective Ia, Ib ou Ic, ledit premier composé contenant un groupe ester d'acide carboxylique dans R², R³ ou R⁵, le procédé consistant à convertir le groupe ester d'acide carboxylique en le groupe carboxy correspondant.
5. Procédé suivant la revendication 4, qui consiste à convertir le groupe ester d'acide carboxylique en le

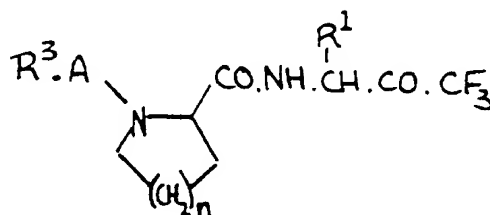
groupe carboxy correspondant par hydrolyse.

6. Procédé suivant la revendication 1 ou la revendication 4, qui consiste en outre à former un troisième composé de formule Ia, Ib ou Ic contenant un groupe sulfonylaminocarbonyle dans R², R³ ou R⁵ à partir du premier ou du second composé de formule respective Ia, Ib ou Ic, ledit premier ou second composé contenant un groupe carboxy dans R², R³ ou R⁵, par couplage dudit groupe carboxy avec le groupe amino d'un sulfonamide.
7. Procédé suivant la revendication 6, qui comprend un couplage impliquant au choix l'utilisation de l'une ou l'autre des possibilités suivantes :
- (a) chlorhydrate de 1-éthyl-3-(3-diméthylaminopropyl)carbodiimide et 4-diméthylaminopyridine dans le chlorure de méthylène ; et
 - (b) 1,3-dicyclohexylcarbodiimide et 4-diméthylaminopyridine dans le chlorure de méthylène.

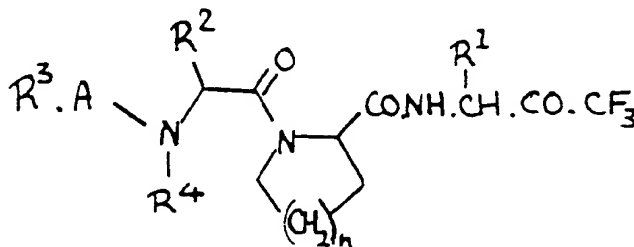
15 Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

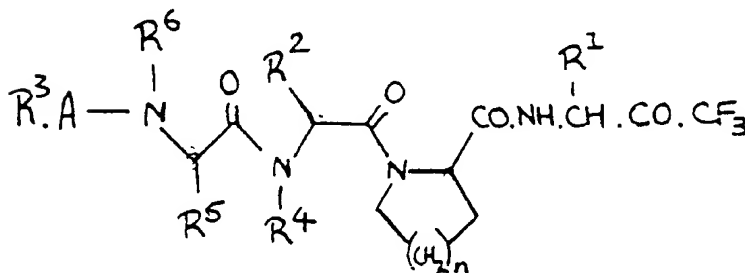
1. Verbindung der Formel Ia, Ib oder Ic,



Ia



Ib



Ic

worin

R¹ für eine Alkyl-Gruppe mit 1 bis 5 Kohlenstoffatomen und vorzugsweise 2 bis 5 Kohlenstoffatomen steht;

R² und R⁵ jeweils unabhängig ausgewählt sind aus:

(I) einer Alkyl-Gruppe mit 1 bis 10 Kohlenstoffatomen;

(II) einer Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, die durch mindestens ein Mitglied aus der folgenden Gruppe substituiert ist:

(a) Hydroxy;

- (b) Amino;
- (c) Alkylamino mit 1 bis 6 Kohlenstoffatomen;
- (d) Dialkylamino, worin jede Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (e) Alkanoyl mit 1 bis 6 Kohlenstoffatomen;
- 5 (f) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;
- (g) Aralkanoyl mit 8 bis 13 Kohlenstoffatomen;
- (h) Amido, welches an die Alkyl-Gruppe über entweder ein Stickstoffatom oder ein Kohlenstoffatom von diesem Amido gebunden sein kann;
- (i) Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- 10 (j) Alkylaminocarbonyl, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (k) Arylcarbonylamino, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- (l) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
- (m) Arylaminocarbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- (n) Aralkylaminocarbonyl, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
- 15 (o) Carboxy;
- (p) Aryloxycarbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- (q) Aralkoxycarbonyl, worin die Aralkoxy-Gruppe 7 bis 13 Kohlenstoffatome enthält;
- (r) Alkanoyloxy mit 1 bis 6 Kohlenstoffatomen;
- (s) Aryloxy, worin der Aryl-Teil 6, 10 oder 12 Kohlenstoffatome enthält;
- 20 (t) Aralkanoyloxy mit 8 bis 14 Kohlenstoffatomen;
- (u) Alkylsulfonamido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (v) Aralkylsulfonamido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
- (w) Arylsulfonamido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- (x) Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl), einschließlich Acylsulfonamido, worin die Acyl-Gruppe 1 bis 7 Kohlenstoffatome enthält, wenn sie den Endteil des Acylsulfonamids bildet, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;
- 25 (y) Alkoxycarbonyl, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (z) Aralkoxycarbonylamino, worin die Aralkoxy-Gruppe 8 bis 13 Kohlenstoffatome enthält, (z.B. Benzyloxycarbonylamino);
- (aa) Aryloxycarbonylamino, worin die Aryloxy-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- (bb) Alkoxycarbonylamino, worin die Alkyloxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (cc) Aryl mit 6, 10 oder 12 Kohlenstoffatomen (z.B. Phenyl, Biphenyl, Naphthyl);
- 35 (dd) Aryl mit 6, 10 oder 12 Kohlenstoffatomen und substituiert durch 1 bis 3 Mitglieder aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Trifluoromethyl, Hydroxy, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxycarbonyl (1 bis 6 Kohlenstoffatome), Carboxy, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome), und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;
- 40 (ee) Cycloalkyl mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl);
- (ff) Alkylureido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (gg) Aralkylureido, worin die Aralkyl-Gruppe 8 bis 13 Kohlenstoffatome enthält;
- 45 (hh) Arylureido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält; und
- (III) einer Aryl-Gruppe mit 6 Kohlenstoffatomen, z.B. Phenyl;
- R³ ausgewählt ist aus
- (I) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen;
- (II) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen und 1 bis 4 Heteroatomen, von denen jedes
- 50 unabhängig ausgewählt ist aus Stickstoff und Sauerstoff;
- (III) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen und gegebenenfalls 1 bis 4 Heteroatomen, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff, die an mindestens einem Kohlenstoffatom oder Stickstoffatom durch 1 bis 3 unabhängig aus der folgenden Gruppe ausgewählte Mitglieder substituiert ist:
- 55 Für Kohlenstoff:
- (a) Hydroxy, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A gebunden ist;
- (b) Amino, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A

gebunden ist;

(c) Alkylamino mit 1 bis 6 Kohlenstoffatomen, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A gebunden ist;

(d) Dialkylamino, worin jede Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A gebunden ist;

(e) Alkanoyl mit 1 bis 6 Kohlenstoffatomen;

(f) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;

(g) Aralkanoyl mit 8 bis 13 Kohlenstoffatomen;

(h) Amido, welches an die Alkyl-Gruppe über entweder ein Stickstoffatom oder ein Kohlenstoffatom von diesem Amido gebunden sein kann;

(i) Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(j) Alkylaminocarbonyl, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(k) Arylcarbonylamino, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(k)-(1) Arylcarbonylamino, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Carboxy, Alkoxy, Carbonyl, worin das Alkoxy 1 bis 3 Kohlenstoffatome enthält, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonaminocarbonyl) mit 1 bis 15 Kohlenstoffatomen substituiert ist, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(l) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(l)-(1) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Carboxy, Alkoxy, Carbonyl, worin das Alkoxy 1 bis 3 Kohlenstoffatome enthält, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonaminocarbonyl) mit 1 bis 15 Kohlenstoffatomen substituiert ist, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(m) Arylaminocarbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(n) Aralkylaminocarbonyl, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(o) Carboxy;

(p) Aryloxy, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(q) Aralkoxy, worin die Aralkoxy-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(r) Alkanoyloxy mit 1 bis 6 Kohlenstoffatomen;

(s) Aroyloxy, worin der Aryl-Teil 6, 10 oder 12 Kohlenstoffatome enthält;

(t) Aralkanoyloxy mit 8 bis 13 Kohlenstoffatomen;

(u) Alkylsulfonamido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(u)-(1) Cycloalkylsulfonamido, worin der Cycloalkyl-Teil 3 bis 15 Kohlenstoffatome enthält, (z.B. Cyclohexyl, Adamantyl, Norbornyl);

(v) Aralkylsulfonamido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(w) Arylsulfonamido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(x) Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonaminocarbonyl) (1 bis 15 Kohlenstoffatome), einschließlich Acylsulfonamido, worin die Acyl-Gruppe 1 bis 7 Kohlenstoffatome enthält, wenn sie den Endteil des Acylsulfonamids bildet, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(y) Alkoxy, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(z) Aralkoxy, worin die Aralkoxy-Gruppe 8 bis 13 Kohlenstoffatome enthält, (z.B. Benzyloxy, Carbonyloxy);

(z)-(1) Aralkylaminocarbonyloxy, worin die Aralkyl-Gruppe 8 bis 13 Kohlenstoffatome enthält;

(z)-(2) Aryloxy, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;

(z)-(3) Aryloxy, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Aminocarbonyl, Aminocarbonylalkyl, worin das Alkyl 1 bis 3 Kohlenstoffatome enthält, Alkoxy, Carbonyl mit 1 bis 3 Kohlenstoffatome und Carboxy substituiert ist;

(aa) Aryloxy, worin die Aryloxy-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(aa)-(1) Arylaminocarbonyloxy, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(bb) Alkoxy, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(bb)-(1) Alkoxy, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält und gegebenenfalls mit einem Kohlenstoffatom an ein Kohlenstoffatom einer aromatischen heterocyclischen Gruppe gebunden ist, wie sie in (gg) unter R³ beschrieben ist;

(bb)-(2) Alkoxy-carbonylamino, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält und durch eine aliphatische heterocyclische Gruppe substituiert ist, wie sie in (ff) unter R³ beschrieben ist;

(bb)-(3) Aryloxyalkyl-carbonylamino, worin das Aryl 6 oder 10 Kohlenstoffatome und das Alkyl 1 bis 6 Kohlenstoffatome enthält;

(bb)-(4) Alkylaminocarbonyloxy, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(cc) Aryl mit 6, 10 oder 12 Kohlenstoffatomen (z.B. Phenyl, Naphthyl, Biphenyl);

(cc)-(1) Aryloxy mit 6, 10 oder 12 Kohlenstoffatomen;

(dd) Aryl mit 6, 10 oder 12 Kohlenstoffatomen und substituiert durch 1 bis 3 Mitglieder, die unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy-carbonyl (2 bis 6 Kohlenstoffatome), Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome) ausgewählt sind, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(dd)-(1) Aryloxy mit 6, 10 oder 12 Kohlenstoffatomen und substituiert an Kohlenstoff durch 1 bis 3 Mitglieder, die unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy-carbonyl (2 bis 6 Kohlenstoffatome), Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo, Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome) ausgewählt sind, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(ee) Cycloalkyl mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl);

(ee)-(1) Cycloalkyloxy mit 3 bis 15 Kohlenstoffatomen;

(ff) eine aliphatische heterocyclische Gruppe mit mindestens 4 Atomen, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff, (z.B. Morpholin, Piperazin), worin die aliphatische heterocyclische Gruppe gegebenenfalls 1 oder 2 Doppelbindungen enthalten kann, welche aliphatische heterocyclische Gruppe an irgendeinem Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkanoyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Aryloxy-carbonyl-Gruppe, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält, eine Aralkyloxy-carbonyl-Gruppe, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält, oder eine Alkoxy-carbonyl-Gruppe, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, substituiert sein kann;

(ff)-(1) eine aliphatische heterocyclische Oxy-Gruppe, worin die Oxy-Gruppierung direkt an ein Kohlenstoffatom der aliphatischen heterocyclischen Gruppe mit mindestens 5 Atomen gebunden ist, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff, (z.B. Morpholin, Piperazin), worin die aliphatische heterocyclische Gruppe gegebenenfalls 1 oder 2 Doppelbindungen enthalten kann, welche aliphatische heterocyclische Gruppe an irgendeinem Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkanoyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Aryloxy-carbonyl-Gruppe, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält, eine Aralkyloxy-carbonyl-Gruppe, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält, oder eine Alkoxy-carbonyl-Gruppe, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, substituiert sein kann;

(gg) eine aromatische heterocyclische Gruppe, die folgendes enthält: (1) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig ausgewählt ist aus Schwefel, Stickstoff und Sauerstoff, und (2) 1 bis 3 fünf- oder sechsgliedrige Ringe, von denen mindestens einer aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen, Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome) und Aminocarbonyl substituiert sein können, und mit der weiteren Maßgabe, daß jedes Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann;

(gg)-(1) eine aromatische heterocyclische Oxy-Gruppe, worin die Oxy-Gruppierung direkt an ein Kohlenstoffatom einer aromatischen heterocyclischen Gruppe gebunden ist, die folgendes enthält: (1) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig ausgewählt

ist aus Schwefel, Stickstoff und Sauerstoff, und (2) 1 bis 3 fünf- oder sechsgliedrige Ringe, von denen mindestens einer aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen, Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome) und Aminocarbonyl substituiert sein können, und mit der weiteren Maßgabe, daß jedes Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann;

(hh) Alkylureido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(hh)-(1) Cycloalkylureido, worin die Alkyl-Gruppe 3 bis 15 Kohlenstoffatome enthält;

(ii) Aralkylureido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(jj) Arylureido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(jj)-(1) Arylureido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält und durch 1 bis 3 Mitglieder substituiert ist, die unabhängig ausgewählt sind aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy-carbonyl (2 bis 6 Kohlenstoffatome), Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome), einschließlich Acylsulfonamido, worin die Acyl-Gruppe 1 bis 7 Kohlenstoffatome enthält, wenn sie den Endteil des Acylsulfonamids bildet, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

Für Stickstoff:

(a) Alkyl mit 1 bis 3 Kohlenstoffatomen;

(b) Alkanoyl mit 2 bis 6 Kohlenstoffatomen;

(c) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;

(d) Aralkanoyl mit 8 bis 14 Kohlenstoffatomen;

(e) Formyl;

(f) eine aliphatische heterocyclische Gruppe, worin die Amino-Gruppierung direkt an ein Kohlenstoffatom einer aliphatischen heterocyclischen Gruppe gebunden ist, die in (ff) für die Kohlenstoff-Substituenten definiert ist;

(g) eine aromatische heterocyclische Gruppe, worin die Amino-Gruppierung direkt an ein Kohlenstoffatom der aromatischen heterocyclischen Gruppe gebunden ist, die in (gg) für die Kohlenstoff-Substituenten definiert ist;

(IV) einer Aryl-Gruppe mit 6, 10 oder 12 Kohlenstoffen;

(V) einer Aryl-Gruppe mit 6, 10 oder 12 Kohlenstoffatomen, die in geeigneter Weise durch 1 bis 3 Mitglieder substituiert ist, die unabhängig ausgewählt sind aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Hydroxy, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkoxy-carbonyl mit 2 bis 6 Kohlenstoffatomen, Carboxy, Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) mit 1 bis 15 Kohlenstoffatomen, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(VI) einer Cycloalkyl-Gruppe mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl);

(VI)-(1) einer Cycloalkyl-Gruppe mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl), die durch ein Mitglied aus der Gruppe Carboxy und Alkoxy-carbonyl, worin die Alkoxy-Gruppe 1 bis 4 Kohlenstoffatome enthält, substituiert ist;

(VII) einer aliphatischen heterocyclischen Gruppe mit mindestens 5 Atomen, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig aus Stickstoff und Sauerstoff ausgewählt ist, (z.B. Morpholin, Piperazin), welche an irgendeinem Stickstoffatom durch ein Mitglied aus der Gruppe Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 1 bis 6 Kohlenstoffatomen, Aryloxycarbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält, Aralkoxycarbonyl, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält, und Alkoxy-carbonyl mit 2 bis 7 Kohlenstoffatomen substituiert sein kann, mit der Maßgabe, daß, wenn A für OCO oder NHCO steht, das A an ein Kohlenstoffatom der aliphatischen heterocyclischen Gruppe gebunden sein muß;

(VIII) einer aromatischen heterocyclischen Gruppe, die folgendes enthält: (a) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig aus Schwefel, Stickstoff und Sauerstoff ausgewählt ist, und (b) 1 bis 3 fünf- oder sechsgliedrige Ringe, von denen mindestens einer

aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe an irgendeinem Kohlenstoffatom durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen und Carboxy substituiert sein können, und mit der weiteren Maßgabe, daß jeder Stickstoff durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann, und daß, wenn A für OCO oder NHCO steht, das A an ein Kohlenstoffatom der aromatischen heterocyclischen Gruppe gebunden sein muß;

(IX) einer Alkenyl-Gruppe mit 2 bis 10 Kohlenstoffatomen und mit mindestens einer Doppelbindung; und

(X) einer Alkenyl-Gruppe mit 2 bis 10 Kohlenstoffatomen und mit mindestens einer Doppelbindung, die durch ein aus der folgenden Gruppe ausgewähltes Mitglied substituiert ist:

(a) Aryl mit 6 oder 10 Kohlenstoffatomen;

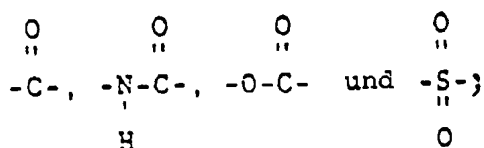
(b) Aryl mit 6 oder 10 Kohlenstoffatomen, das durch 1 bis 3 Mitglieder substituiert ist, die unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxycarbonyl (2 bis 6 Kohlenstoffatome), Carboxy, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome) ausgewählt sind, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann; und

(c) Ureidocarbonyl;

R⁴ und R⁵ unabhängig ausgewählt sind aus Wasserstoff oder Methyl;

n für 0, 1 oder 2 steht; und

A ausgewählt ist aus



oder, sofern geeignet, ein Säure- oder Basenadditionssalz davon; mit der Maßgabe, daß,

1. Alkyle gerade oder verzweigt sein können;

2. kein Kohlenstoffatom eines Alkyls direkt an zwei Heteroatome gebunden sein kann;

3. kein Heteroatom direkt an Schwefel, Stickstoff oder Sauerstoff gebunden sein; und

4. Alkenyle von (IX) und (X) für R³ nicht 1,1-disubstituiert sein können und ein Kohlenstoff einer Doppelbindung nicht direkt an Sauerstoff oder Stickstoff gebunden sein kann.

2. Verbindung nach Anspruch 1, worin

R¹ für eine Alkyl-Gruppe mit 3 Kohlenstoffatomen steht;

R² und R⁵ jeweils unabhängig ausgewählt sind aus:

(I) einer Alkyl-Gruppe mit 1 bis 4 Kohlenstoffatomen;

(II) einer Alkyl-Gruppe mit 1 bis 4 Kohlenstoffatomen, die durch mindestens ein Mitglied aus der folgenden Gruppe substituiert ist:

(e) Alkanoyl mit 1 bis 3 Kohlenstoffatomen;

(f) Arylcarbonyl, worin das Aryl 6 oder 10 Kohlenstoffatomen enthält;

(g) Aralkanoyl mit 8 Kohlenstoffatomen;

(h) Amido, welches an die Alkyl-Gruppe über entweder ein Stickstoffatom oder ein Kohlenstoffatom von diesem Amido gebunden sein kann;

(i) Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 2 Kohlenstoffatome enthält;

(j) Alkylaminocarbonyl, worin die Alkyl-Gruppe 1 bis 2 Kohlenstoffatome enthält;

(k) Arylcarbonylamino, worin die Aryl-Gruppe 6 Kohlenstoffatome enthält;

(l) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 Kohlenstoffatome enthält;

(m) Arylaminocarbonyl, worin die Aryl-Gruppe 6 Kohlenstoffatome enthält;

(n) Aralkylaminocarbonyl, worin die Aralkyl-Gruppe 7 Kohlenstoffatome enthält;

(o) Carboxy;

- (p) Aryloxycarbonyl, worin die Aryl-Gruppe 6 Kohlenstoffatome enthält;
 (q) Aralkoxycarbonyl, worin die Aralkoxy-Gruppe 7 Kohlenstoffatome enthält;
 (r) Alkanoyloxy mit 1 bis 2 Kohlenstoffatomen;
 (s) Aroyloxy, worin der Aryl-Teil 6 Kohlenstoffatome enthält;
 5 (t) Aralkanoyloxy mit 8 Kohlenstoffatomen;
 (u) Alkylsulfonamido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 (v) Aralkylsulfonamido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (w) Arylsulfonamido, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält;
 (x) Acylsulfonamido mit 1 bis 15 Kohlenstoffatomen;
 10 (y) Alkoxycarbonyl, worin die Alkoxy-Gruppe 1 bis 2 Kohlenstoffatome enthält;
 (z) Aralkoxycarbonylamino, worin die Aralkoxy-Gruppe 7 Kohlenstoffatome enthält;
 (aa) Aryloxycarbonylamino, worin die Aryloxy-Gruppe 6 Kohlenstoffatome enthält;
 (bb) Alkoxycarbonylamino, worin die Alkyloxy-Gruppe 1 bis 3 Kohlenstoffatome enthält;
 (cc) Aryl mit 6 oder 10 Kohlenstoffatomen;
 15 (dd) Aryl mit 6 oder 10 Kohlenstoffatomen und substituiert durch 1 bis 3 Mitglieder aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Trifluoromethyl, Hydroxy, Alkyl (1 bis 2 Kohlenstoffatome), Alkoxy (1 bis 2 Kohlenstoffatome), Alkoxycarbonyl (2 bis 3 Kohlenstoffatome), Carboxy, 5-Tetrazolo und Acylsulfonamido (1 bis 15 Kohlenstoffatome);
 (ee) Cycloalkyl mit 3 bis 15 Kohlenstoffatomen;
 20 (ff) Alkylureido, worin die Alkyl-Gruppe 1 bis 2 Kohlenstoffatome enthält;
 (gg) Aralkylureido, worin die Aralkyl-Gruppe 7 Kohlenstoffatome enthält;
 (hh) Arylureido, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält; und
 (III) einer Aryl-Gruppe mit 6 Kohlenstoffatomen;
 R³ ausgewählt ist aus
 25 (I) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen;
 (II) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen und 1 bis 4 Heteroatomen, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff;
 (III) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen und gegebenenfalls 1 bis 4 Heteroatomen, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff, die an mindestens einem Kohlenstoffatom oder Stickstoffatom durch 1 bis 3 unabhängig aus der folgenden Gruppe ausge-
 30 wählte Mitglieder substituiert ist:
 Für Kohlenstoff:
 (e) Alkanoyl mit 1 bis 6 Kohlenstoffatomen;
 (f) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;
 35 (g) Aralkanoyl mit 8 bis 13 Kohlenstoffatomen;
 (h) Amido, welches an die Alkyl-Gruppe über entweder ein Stickstoffatom oder ein Kohlenstoffatom von diesem Amido gebunden sein kann;
 (i) Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 (j) Alkylaminocarbonyl, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 40 (k) Arylcarbonylamino, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält;
 (k)-(1) Arylcarbonylamino, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Carboxy, Alkoxycarbonyl, worin das Alkoxy 1 bis 3 Kohlenstoffatome enthält, 5-Tetrazolo, und Acylsulfonamido mit 1 bis 15 Kohlenstoffatomen substituiert ist;
 (l) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 45 (l)-(1) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Carboxy, Alkoxycarbonyl, worin das Alkoxy 1 bis 3 Kohlenstoffatome enthält, 5-Tetrazolo, und Acylsulfonamido mit 1 bis 15 Kohlenstoffatomen substituiert ist;
 (m) Arylaminocarbonyl, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält;
 50 (n) Aralkylaminocarbonyl, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (o) Carboxy;
 (p) Aryloxycarbonyl, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält;
 (q) Aralkoxycarbonyl, worin die Aralkoxy-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (r) Alkanoyloxy mit 2 bis 3 Kohlenstoffatomen;
 55 (s) Aroyloxy, worin der Aryl-Teil 6 oder 10 Kohlenstoffatome enthält;
 (t) Aralkanoyloxy mit 8 bis 13 Kohlenstoffatomen;
 (u) Alkylsulfonamido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 (u)-(1) Cycloalkylsulfonamido, worin der Cycloalkyl-Teil 3 bis 15 Kohlenstoffatome enthält;

- (v) Aralkylsulfonamido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (w) Arylsulfonamido, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält;
 (x) Acylsulfonamido mit 1 bis 15 Kohlenstoffatomen;
 (y) Alkoxycarbonyl, worin die Alkoxy-Gruppe 1 bis 3 Kohlenstoffatome enthält;
 5 (z) Aralkoxycarbonylamino, worin die Aralkoxy-Gruppe 8 bis 13 Kohlenstoffatome enthält;
 (z)-(1) Aralkylaminocarbonyloxy, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (z)-(2) Aryloxy, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;
 (z)-(3) Aryloxy, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält und durch ein Mitglied aus
 10 der Gruppe Aminocarbonyl, Aminocarbonylalkyl, worin das Alkyl 1 bis 3 Kohlenstoffatome enthält,
 Alkoxycarbonyl mit 2 bis 4 Kohlenstoffatomen und Carboxy substituiert ist;
 (aa) Aryloxycarbonylamino, worin die Aryloxy-Gruppe 6 oder 10 Kohlenstoffatome enthält;
 (aa)-(1) Arylaminocarbonyloxy, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält;
 (bb) Alkoxycarbonylamino, worin die Alkyloxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 15 (bb)-(1) Alkoxycarbonylamino, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält und
 gegebenenfalls an ein Kohlenstoffatom einer aromatischen heterocyclischen Gruppe gebunden
 ist, wie sie in (gg) unter R³ beschrieben ist;
 (bb)-(2) Alkoxycarbonylamino, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält und
 durch eine aliphatische heterocyclische Gruppe substituiert ist, wie sie in (ff) unter R³ beschrie-
 ben ist;
 20 (bb)-(3) Aryloxyalkylcarbonylamino, worin das Aryl 6 oder 10 Kohlenstoffatome und das Alkyl 1
 bis 6 Kohlenstoffatome enthält;
 (bb)-(4) Alkylaminocarbonyloxy, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 (cc) Aryl mit 6 oder 10 Kohlenstoffatomen;
 (cc)-(1) Aryloxy mit 6 oder 10 Kohlenstoffatomen;
 25 (dd) Aryl mit 6, 10 oder 12 Kohlenstoffatomen und substituiert durch 1 bis 3 Mitglieder, die
 unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6
 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxycarbonyl (2 bis 6 Kohlenstoffatome),
 Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo und Acylsul-
 fonamido (1 bis 15 Kohlenstoffatome) ausgewählt sind;
 30 (dd)-(1) Aryloxy mit 6, 10 oder 12 Kohlenstoffatomen und substituiert durch 1 bis 3 Mitglieder, die
 unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6
 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxycarbonyl (2 bis 6 Kohlenstoffatome),
 Carboxy, Acylsulfonamido (1 bis 15 Kohlenstoffatome), Aminocarbonylalkyl (2 bis 6 Kohlenstoff-
 atome), Aminocarbonyl und 5-Tetrazolo ausgewählt sind;
 35 (ee) Cycloalkyl mit 3 bis 15 Kohlenstoffatomen;
 (ee)-(1) Cycloalkyloxy mit 3 bis 15 Kohlenstoffatomen;
 (ff) eine aliphatische heterocyclische Gruppe mit mindestens 5 Atomen, die 1 bis 5 Kohlenstoff-
 atome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig ausgewählt ist aus
 40 Stickstoff und Sauerstoff, worin die aliphatische heterocyclische Gruppe gegebenenfalls 1 oder 2
 Doppelbindungen enthalten kann, welche aliphatische heterocyclische Gruppe an irgendeinem
 Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkanoyl-Gruppe mit
 2 bis 6 Kohlenstoffatomen, eine Aryloxycarbonyl-Gruppe, worin die Aryl-Gruppe 6, 10 oder 12
 Kohlenstoffatome enthält, eine Aralkyloxycarbonyl-Gruppe, worin die Aralkyl-Gruppe 7 bis 13
 Kohlenstoffatome enthält, oder eine Alkoxycarbonyl-Gruppe, worin die Alkyl-Gruppe 1 bis 6
 45 Kohlenstoffatome enthält, substituiert sein kann;
 (ff)-(1) eine aliphatische heterocyclische Oxy-Gruppe, worin die Oxy-Gruppierung direkt an ein
 Kohlenstoffatom einer aliphatischen heterocyclischen Gruppe mit mindestens 5 Atomen gebunden
 ist, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig
 ausgewählt ist aus Stickstoff und Sauerstoff, worin die aliphatische heterocyclische Gruppe
 50 gegebenenfalls 1 oder 2 Doppelbindungen enthalten kann, welche aliphatische heterocyclische
 Gruppe an irgendeinem Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen,
 eine Alkanoyl-Gruppe mit 2 bis 6 Kohlenstoffatomen, eine Aryloxycarbonyl-Gruppe, worin die
 Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält, eine Aralkyloxycarbonyl-Gruppe, worin die
 Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält, oder eine Alkoxycarbonyl-Gruppe, worin die
 55 Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, substituiert sein kann;
 (gg) eine aromatische heterocyclische Gruppe, die folgendes enthält: (1) 1 bis 15 Kohlenstoffato-
 me und 1 bis 4 Heteroatome, von denen jedes unabhängig ausgewählt ist aus Schwefel,
 Stickstoff und Sauerstoff, und (2) 1 bis 2 fünf- oder sechsgliedrige Ringe, von denen mindestens

- einer aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl, das Methyl enthält, Alkoxy mit 1 bis 2 Kohlenstoffatomen, Alkanoyl mit 2 bis 3 Kohlenstoffatomen, Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome) und Aminocarbonyl substituiert sein können, und mit der weiteren Maßgabe, daß jedes Stickstoffatom durch eine Alkyl-Gruppe mit bis 1 bis 6 Kohlenstoffatomen substituiert sein kann;
- (gg)-(1) eine aromatische heterocyclische Oxy-Gruppe, worin die Oxy-Gruppierung direkt an ein Kohlenstoffatom einer aromatischen heterocyclischen Gruppe gebunden ist, die folgendes enthält: (1) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig ausgewählt ist aus Schwefel, Stickstoff und Sauerstoff, und (2) 1 bis 2 fünf- oder sechsgliedrige Ringe, von denen mindestens einer aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Methyl, Alkoxy mit 1 bis 2 Kohlenstoffatomen, Alkanoyl mit 2 bis 3 Kohlenstoffatomen, Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome) und Aminocarbonyl substituiert sein können, und mit der weiteren Maßgabe, daß jedes Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein;
- (hh) Alkylureido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (hh)-(1) Cycloalkylureido, worin die Alkyl-Gruppe 3 bis 15 Kohlenstoffatome enthält;
- (ii) Aralkylureido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
- (jj) Arylureido, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält;
- (jj)-(1) Arylureido, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält und durch 1 bis 3 Mitglieder substituiert ist, die unabhängig ausgewählt sind aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxycarbonyl (2 bis 6 Kohlenstoffatome), Carboxy, Acylsulfonamido (1 bis 15 Kohlenstoffatome), Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl und 5-Tetrazolo;
- Für Stickstoff:
- (a) Alkyl mit 1 bis 3 Kohlenstoffatomen;
- (b) Alkanoyl mit 2 bis 6 Kohlenstoffatomen;
- (c) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;
- (d) Aralkanoyl mit 8 bis 13 Kohlenstoffatomen;
- (e) Formyl;
- (f) eine aliphatische heterocyclische Amino-Gruppe, worin die Amino-Gruppierung direkt an ein Kohlenstoffatom einer aliphatischen heterocyclischen Gruppe gebunden ist, die in (ff) für die Kohlenstoff-Substituenten definiert ist;
- (g) eine aromatische heterocyclische Amino-Gruppe, worin die Amino-Gruppierung direkt an ein Kohlenstoffatom der aromatischen heterocyclischen Gruppe gebunden ist, die in (gg) für die Kohlenstoff-Substituenten definiert ist;
- (IV) einer Aryl-Gruppe mit 6 oder 10 Kohlenstoffatomen;
- (V) einer Aryl-Gruppe mit 6 oder 10 Kohlenstoffatomen, die in geeigneter Weise durch 1 bis 3 Mitglieder substituiert ist, die unabhängig ausgewählt sind aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkoxycarbonyl mit 2 bis 6 Kohlenstoffatomen, Carboxy, Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, 5-Tetrazolo und Acylsulfonamido mit 1 bis 15 Kohlenstoffatomen;
- (VI) einer Cycloalkyl-Gruppe mit 3 bis 15 Kohlenstoffatomen;
- (VI)-(1) einer Cycloalkyl-Gruppe mit 3 bis 15 Kohlenstoffatomen, die durch ein Mitglied aus der Gruppe Carboxy und Alkoxycarbonyl, worin die Alkoxy-Gruppe 1 bis 4 Kohlenstoffatome enthält, substituiert ist;
- (VII) einer aliphatischen heterocyclischen Gruppe mit mindestens 5 Atomen, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig aus Stickstoff und Sauerstoff ausgewählt ist, welche an irgendeinem Stickstoffatom durch ein Mitglied aus der Gruppe Methyl, Alkanoyl mit 2 bis 6 Kohlenstoffatomen, Aryloxycarbonyl, worin die Aryl-Gruppe 6 oder 10 Kohlenstoffatome enthält, Aralkoxycarbonyl, worin die Aralkyl-Gruppe 7 Kohlenstoffatome enthält, und Alkoxycarbonyl mit 2 bis 3 Kohlenstoffatomen substituiert sein kann, mit der Maßgabe, daß, wenn A für OCO oder NHCO steht, das A an ein Kohlenstoff der aliphatischen heterocyclischen Gruppe gebunden sein muß;
- (VIII) einer aromatischen heterocyclischen Gruppe, die folgendes enthält: (a) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig aus Schwefel, Stickstoff und Sauerstoff ausgewählt ist, und (b) 1 bis 2 fünf- oder sechsgliedrige Ringe, von denen mindestens einer

aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe an irgendeinem Kohlenstoffatom durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Methyl, Alkoxy mit 1 bis 2 Kohlenstoffatomen, Alkanoyl mit 2 bis 3 Kohlenstoffatomen und Carboxy substituiert sein können, und mit der weiteren Maßgabe, daß jeder Stickstoff durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann, und daß, wenn A für OCO oder NHCO steht, das A an ein Kohlenstoffatom der aromatischen heterocyclischen Gruppe gebunden sein muß;

(IX) einer Alkenyl-Gruppe mit 2 bis 10 Kohlenstoffatomen und mit mindestens einer Doppelbindung;
(X) einer Alkenyl-Gruppe mit 2 bis 10 Kohlenstoffatomen und mit mindestens einer Doppelbindung, die durch ein aus der folgenden Gruppe ausgewähltes Mitglied substituiert ist;

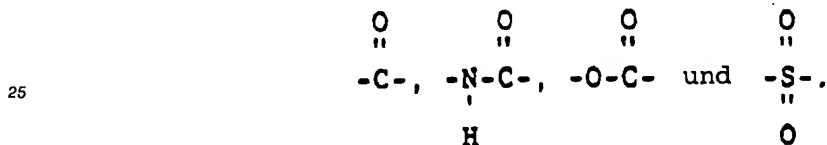
- (a) Aryl mit 6 oder 10 Kohlenstoffatomen;
(b) Aryl mit 6 oder 10 Kohlenstoffatomen, das durch 1 bis 3 Mitglieder substituiert ist, die unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxycarbonyl (2 bis 6 Kohlenstoffatome); Carboxy, Acylsulfonamido (1 bis 15 Kohlenstoffatome) und 5-Tetrazolo ausgewählt sind; und
(c) Ureidocarbonyl;

R⁴ und R⁵ jeweils für Wasserstoff stehen;

n für 1 steht; und

A ausgewählt ist aus

20



30 3. Verbindung nach Anspruch 1,
worin

R¹ für Isopropyl steht;

R² ausgewählt ist aus:

(I) einer Alkyl-Gruppe mit 2 bis 3 Kohlenstoffatomen;
35 (II) (q) Ethyl, das durch Aralkoxycarbonyl substituiert ist, worin die Aralkoxy-Gruppe 7 Kohlenstoffatome enthält;

(w) Butyl, das durch Arylsulfonamido substituiert ist, worin der Aryl-Teil 6 Kohlenstoffatome enthält;

(x) Ethyl, das durch Acylsulfonamido mit 7 Kohlenstoffatomen substituiert ist;

40 (z) Butyl, das durch Aralkyloxycarbonylamino substituiert ist, worin der Aralkoxy-Teil 7 Kohlenstoffatome enthält;

(cc) Methyl, das durch Aryl mit 6 Kohlenstoffatomen substituiert ist;

(III) Aryl mit 6 Kohlenstoffatomen;

R³ ausgewählt ist aus:

45 (I) verzweigtem Alkyl mit 4 Kohlenstoffatomen;

(II) einer Alkyl-Gruppe mit 5 Kohlenstoffatomen und 2 Sauerstoffatomen;

(III) (k) Ethyl, das durch Arylcarbonylamino substituiert ist, worin der Aryl-Teil 6 Kohlenstoffatome enthält;

50 (l) Ethyl, das durch Aralkylcarbonylamino substituiert ist, worin der Aralkyl-Teil 13 Kohlenstoffatome enthält;

(n) Ethyl, das durch Aralkylaminocarbonyl substituiert ist, worin der Alkyl-Teil 7 Kohlenstoffatome enthält;

(o) einer Alkyl-Gruppe mit 2 oder 10 Kohlenstoffatomen und substituiert durch Carboxy;

55 (w) einer Alkyl-Gruppe mit 5 Kohlenstoffatomen und substituiert durch Arylsulfonamido, worin der Aryl-Teil 6 Kohlenstoffatome enthält;

(x) Ethyl, das durch Acylsulfonamido substituiert ist, welches ausgewählt ist aus der Gruppe 2-(Methylsulfonylamino)carbonyl)ethyl, 2-(Phenylsulfonylamino)carbonyl)ethyl, 2-[(1-Adamantyl)sulfonylamino)carbonyl)ethyl und 2-[(1-Naphthyl)sulfonylamino)carbonyl)ethyl;

- (y) einer Alkyl-Gruppe mit 2 oder 10 Kohlenstoffatomen und substituiert durch Methoxycarbonyl;
 (z) einer Alkyl-Gruppe mit 2 bis 5 Kohlenstoffatomen und substituiert durch Aralkoxycarbonyl, worin der Aralkoxy-Teil 7 Kohlenstoffatome enthält;
 (aa) einer Alkyl-Gruppe mit 5 Kohlenstoffatomen und substituiert durch Aryloxycarbonylamino, worin der Aryloxy-Teil 6 Kohlenstoffatome enthält;
 (bb) Ethyl, das durch Alkoxycarbonylamino substituiert ist, worin die Alkyl-Gruppe 4 Kohlenstoffatome enthält; und einer Alkyl-Gruppe mit 5 Kohlenstoffatomen und substituiert durch Alkylloxycarbonylamino, worin die Alkoxy-Gruppe 2 Kohlenstoffatome enthält und an endständigen Kohlenstoffatom über eine direkte Bindung mit einem Kohlenstoffatom einer aromatischen heterocyclischen Gruppe mit 5 Kohlenstoffatomen und 1 Stickstoffatom substituiert ist;
 (bb)-(3) Propyl, das durch Aryloxyalkylcarbonylamino substituiert ist, worin die Aryl-Gruppe 6 Kohlenstoffatome enthält und die Alkyl-Gruppe aus Methyl besteht;
 (cc) Methyl oder Butyl, das durch Aryl mit 6 Kohlenstoffatomen substituiert ist; und einer verzweigten Alkyl-Gruppe mit 5 Kohlenstoffatomen und substituiert durch 2 Aryl-Gruppen mit jeweils 6 Kohlenstoffatomen;
 (dd) einem Mitglied aus der Gruppe Alkyl mit 1 oder 2 Kohlenstoffatomen und substituiert durch Aryl mit 6 Kohlenstoffatomen, worin das Aryl weiter durch Carboxy substituiert ist; Methyl, das durch Aryl mit 6 Kohlenstoffatomen substituiert ist, worin das Aryl weiter durch Methoxycarbonyl substituiert ist; Ethyl, das durch Aryl mit 6 Kohlenstoffatomen substituiert ist, worin das Aryl weiter durch Ethoxycarbonyl substituiert ist; und Ethyl, das durch Aryl mit 6 Kohlenstoffatomen substituiert ist, worin das Aryl weiter durch Acylsulfonamido mit 7 Kohlenstoffatomen substituiert ist;
 (ee) Ethyl, das durch Cycloalkyl mit 10 Kohlenstoffatomen substituiert ist;
 (ff) Ethyl, das durch eine aliphatische heterocyclische Gruppe mit 4 Kohlenstoffatomen, 1 Stickstoffatom und 1 Sauerstoffatom substituiert ist;
 (gg) einer Alkyl-Gruppe mit 1 bis 2 Kohlenstoffatomen und substituiert durch eine aromatische heterocyclische Gruppe mit 4 Kohlenstoffatomen und 1 Schwefelatom; und Ethyl, das durch eine aromatische heterocyclische Gruppe mit 5 Kohlenstoffatomen und 1 Stickstoffatom substituiert ist;
 (ji)-(1) einer Alkyl-Gruppe mit 5 Kohlenstoffatomen und substituiert durch Arylureido, worin der Aryl-Teil 6 Kohlenstoffatome enthält und worin der Aryl-Teil weiter durch Ethoxycarbonyl oder Carboxy substituiert ist;
 (zz) Propyl, das durch Aryloxy substituiert ist, worin der Aryl-Teil 6 Kohlenstoffatome enthält; einer verzweigten Alkyl-Gruppe mit 5 Kohlenstoffatomen und substituiert durch 2 Aryloxy-Gruppen, von denen jede 6 Kohlenstoffatome enthält;
 (zzz) Methyl oder Propyl, das durch Aryloxy mit 6 Kohlenstoffatomen substituiert ist, worin das Aryloxy weiter durch Aminocarbonyl substituiert ist; und Methyl, das durch Aryloxy mit 6 Kohlenstoffatomen substituiert ist, worin das Aryloxy weiter durch Ethoxycarbonyl substituiert ist;
 (IV) einer Aryl-Gruppe mit 6 oder 10 Kohlenstoffatomen;
 (V) einer Aryl-Gruppe mit 6 Kohlenstoffatomen, die durch ein Mitglied aus der Gruppe Fluoro, Hydroxy, Carboxy, Methoxy, Ethoxy, Methoxycarbonyl, Ethoxycarbonyl, Methylcarbonylamino, Acylsulfonamido mit 2 Kohlenstoffatomen, Acylsulfonamido mit 7 Kohlenstoffatomen, Acylsulfonamido mit 11 Kohlenstoffatomen, Acylsulfonamido mit 14 Kohlenstoffatomen, Aryl mit 6 Kohlenstoffatomen und substituiert durch zwei Chloro; und Aryl mit 6 Kohlenstoffatomen und substituiert durch ein Chloro und ein Amino substituiert ist;
 (VI) einer Cycloalkyl-Gruppe mit 10 Kohlenstoffatomen;
 (VI)-(1) einer Cycloalkyl-Gruppe mit 5 Kohlenstoffatomen und substituiert durch Carboxy oder Ethoxycarbonyl; und
 (X) einer Alkenyl-Gruppe mit 2 Kohlenstoffatomen und substituiert durch ein Mitglied aus der Gruppe Carboxy, Carboxyphenyl, Ethoxycarbonyl, Ureidocarbonyl, Acylsulfonamido und 4-Carboxyphenyl;
 R⁴ für Wasserstoff steht;
 R⁵ ausgewählt ist aus
 (I) n-Butyl;
 (II) (q) Ethyl, das durch Aralkoxycarbonyl substituiert ist, worin das Aralkoxy 7 Kohlenstoffatome enthält;
 (II) (z) Butyl, das durch Aralkoxycarbonylamino substituiert ist, worin die Aralkyl-Gruppe 7 Kohlenstoffatome enthält;
 A die oben angegebene Bedeutung besitzt; und
 n für 1 steht.

4. Verbindung nach Anspruch 1, welche ausgewählt ist aus

- 1) 3S(oderR)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 2) 3(RS)-[(Phenylmethoxy)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 5 3) 3(RS)-[(4-(Ethoxycarbonyl)phenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 4) 3(RS)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 5) 3(RS)-[(4-Phenylbutyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 10 6) 3(RS)-2[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 7) 3(RS)-[(4-Methoxyphenyl)carbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 8) 3(RS)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 15 9) 3(RS)-[(Phenylmethoxy)carbonyl]-L-phenylalanyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 10) 3(RS)-[2-(Methoxycarbonyl)ethylcarbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 20 11) 3(RS)-[2-(2-Carboxyethyl)carbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 12) 3(RS)-[(Phenylmethoxy)carbonyl]-L-alpha-glutamyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid-phenylmethylester;
- 13) 3(RS)-N²-[2-(Methoxycarbonyl)ethylcarbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 25 14) 3(RS)-N²-[(2-Carboxyethyl)carbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 15) 3S(oderR)-N²,N⁶-Di[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 30 16) 3(RS)-(1-Naphthylcarbonyl)-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 17) 3(RS)-[4-(Methylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 18) 3(RS)-[2-(4-Morpholinyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 35 19) 3(RS)-[(2,4-Dichlorophenyl)carbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 20) 3(RS)-Phenoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 21) 3(RS)-[2-(2-Pyridyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 40 22) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 23) 3(RS)-[2-(3-Thiophenyl)ethoxycarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 24) 3(RS)-(Phenylmethoxycarbonyl)-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 45 25) 3(RS)-(Phenoxycarbonyl)-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 26) 3(RS)-N²-(1,1-Dimethylethoxycarbonyl)-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 50 27) 3(RS)-[2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethoxycarbonyl]-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 28) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-alpha-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 29) 3(RS)-N⁶-Phenylmethoxycarbonyl-N²-phenylsulfonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 55 30) 3(RS)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 31) 3(RS)-Phenylaminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;

- 32) 3(RS)-[[4-[(1-Naphthylsulfonyl)aminocarbonyl] phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 33) 3(RS)-N²-(4-Hydroxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 5 34) 3(RS)-(4-Hydroxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 35) 3(RS)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 36) 3(RS)-(4-Methoxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 10 37) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 38) 3(RS)-(4-Methoxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 15 39) 3(RS)-[E-3-(4-Ethoxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 40) 3(RS)-(2-Ethoxycarbonylphenyl)aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 41) 3(RS)-4-[(4-Nitrophenyl)sulfonylaminocarbonyl]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 20 42) 3(RS)-Phenylmethoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid-phenylmethyl ester;
- 43) 3S(oder R)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 25 44) 3(RS)-Phenylmethoxycarbonyl-L-(5-(phenylsulfonylamino)glutamyl)-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 45) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 46) 3(RS)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 30 47) 3(RS)-4-(1-Naphthylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 48) 3(RS)-[2-(4-Aminocarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 35 49) 3(RS)-(4-Hydroxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 50) 3(RS)-[4-[4-(2-Amino-2-oxoethyl)phenoxy]-1-oxobutyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 51) 3(RS)-E-[3-(4-Hydroxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 40 52) 3(RS)-[2-(4-Ethoxycarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 53) 3(RS)-[3-(4-Ethoxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 45 54) 3(RS)-4-Hydroxybenzoyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 55) 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 56) 3(RS)-[3-(4-Hydroxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 50 57) 3(RS)-[3-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 58) 3(RS)-E-[3-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 59) 3(RS)-[1-[4-[(4-Bromophenyl)sulfonyl][phenylmethyl]aminocarbonyl]phenyl]-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 55 60) 3R(oderS)-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 61) 3S(oderR)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-

- methyl-2-oxopentyl)]-L-prolinamid;
- 62) 3S(oder R)-Phenylmethoxycarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 63) 3S(oder R)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 64) 3S(oder R)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 65) 3S(oder R)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 66) 3S(oder R)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 67) 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 68) 3(RS)-N²,N⁶-Di(phenylmethoxycarbonyl)-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 69) 3(RS)-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 70) 3(RS)-[4-(Methylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 71) 3(RS)-N²-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-N⁶-phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid; und
- 72) 3(RS)-[1,4-Dioxo-4-[(tricyclo[3.3.1.1^{3,7}]dec-1-yl)sulfonylamino]butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid.
5. Verbindung nach Anspruch 4, welche ausgewählt ist aus
- 1) 3(RS)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 2) 3(RS)-[(2-Carboxyethyl)carbonyl]-L-norleucyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 3) 3(RS)-N²-[(2-Carboxyethyl)carbonyl]-N⁶-[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamid;
- 4) 3(RS)-[4-(Methylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 5) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 6) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L- α -aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 7) 3(RS)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 8) 3(RS)-[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 9) 3(RS)-N²-(4-Hydroxycarbonylphenyl)aminocarbonyl-N⁶-phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 10) 3(RS)-(4-Hydroxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 11) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 12) 3(RS)-4-[(4-Nitrophenyl)sulfonylaminocarbonyl]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 13) 3(RS)-Phenylmethoxycarbonyl-L-[5-(phenylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 14) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 15) 3(RS)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 16) 3(RS)-4-(1-Naphthylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
- 17) 3(RS)-(4-Hydroxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-

- pentyl)]-L-prolinamid;
 18) 3(RS)-E-[3-(4-Hydroxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 19) 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 20) 3(RS)-[3-(4-Hydroxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 21) 3(RS)-[3-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 22) 3(RS)-E-[3-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 23) 3S(oderR)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 24) 3S(oderR)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 25) 3S(oderR)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 26) 3S(oderR)-[4-(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 27) 3(RS)-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 28) 3(RS)-[4-(Methylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid; und
 29) 3(RS)-N²-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-N⁶-phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid.

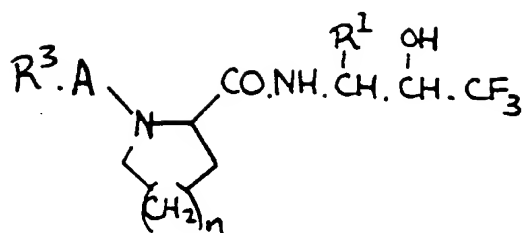
6. Verbindung nach Anspruch 5, welche ausgewählt ist aus

- 1) 3(RS)-[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 2) 3(RS)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 3) 3(RS)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid;
 4) 3S(oderR)-[4-[(4-Bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid; und
 5) 3S(oderR)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamid.

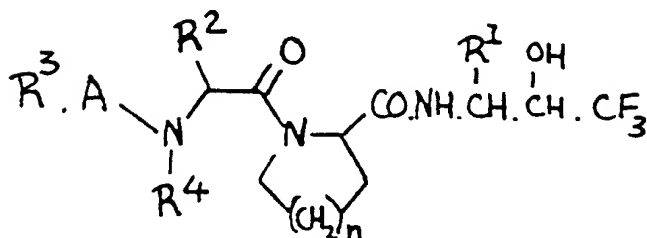
7. Verbindung nach Anspruch 1, bei welcher das Säureadditionssalz mit Salz-, Bromwasserstoff-, Schwefel-, Salpeter-, Zitronen-, Malein-, Fumar- oder Essigsäure gebildet ist.

8. Verbindung nach Anspruch 1, bei welcher das Basenadditionssalz mit einem Alkalimetallhydroxid, einem Alkalimetallcarbonat, einem Alkalimetallbicarbonat, einem Erdalkalimetallhydroxid oder einem organischen Aminsatz gebildet ist.

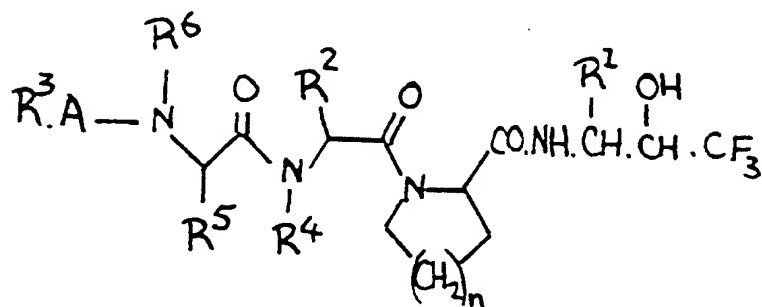
9. Verfahren zur Herstellung der Verbindungen nach einem der Ansprüche 1 bis 8, bei welchem eine Verbindung der Formel VIIa, VIIb oder VIIc



VIIa



VIIb



VIIc

oxidiert wird, wobei eine erste Verbindung der Formel Ia, Ib oder Ic erhalten wird,

10. Verfahren nach Anspruch 9, bei welchem die Oxidation unter Verwendung eines der folgenden Mittel ausgeführt wird:

- (a) Oxalylchlorid, Dimethylsulfoxid und tertiäres Amin in Methylenchlorid;
- (b) Essigsäureanhydrid und Dimethylsulfoxid;
- (c) Chromtrioxid/Pyridin-Komplex in Methylenchlorid; und
- (d) Dess-Martin-Perjodinan in Methylenchlorid.

11. Verfahren nach Anspruch 10, bei welchem die Oxidation unter Verwendung von Dess-Martin-Perjodinan in Methylenchlorid ausgeführt wird.

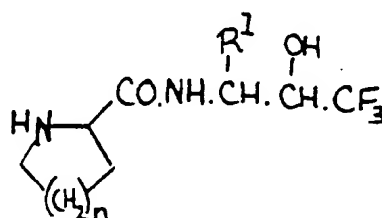
12. Verfahren nach Anspruch 9, bei welchem eine zweite Verbindung der Formel Ia, Ib oder Ic, die eine Carboxy-Gruppe in R², R³ oder R⁵ enthält, aus der genannten ersten Verbindung der Formel Ia, Ib bzw. Ic hergestellt wird, wobei die erste Verbindung eine Carbonsäureester-Gruppe in R², R³ oder R⁵ enthält, bei welchem Verfahren die Carbonsäureester-Gruppe in die entsprechende Carboxy-Gruppe umgewandelt wird.

13. Verfahren nach Anspruch 12, bei welchem die genannte Carbonsäureester-Gruppe durch Hydrolyse in

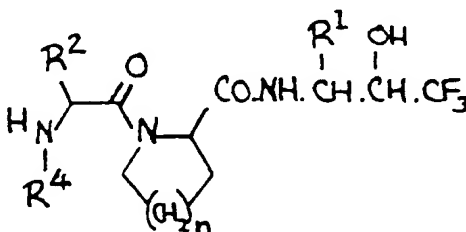
die entsprechende Carboxy-Gruppe überführt wird.

14. Verfahren nach Anspruch 9 oder 12, bei welchem eine dritte Verbindung der Formel Ia, Ib oder Ic, die eine Sulfonylaminocarbonyl-Gruppe in R^2 , R^3 oder R^5 enthält, aus der ersten oder zweiten Verbindung der Formel Ia, Ib bzw. Ic, wobei die erste oder zweite Verbindung eine Carboxy-Gruppe in R^2 , R^3 oder R^5 enthält, durch Kuppeln dieser Carboxy-Gruppe mit der Amino-Gruppe eines Sulfonamids hergestellt wird.
15. Verfahren nach Anspruch 14, bei welchem das Kupplungs-Verfahren mit einem der folgenden Mittel ausgeführt wird:
- (a) 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimidhydrochlorid und 4-Dimethylaminopyridin in Methylenchlorid; und
 - (b) 1,3-Dicyclohexylcarbodiimid und 4-Dimethylaminopyridin in Methylenchlorid.
16. Pharmazeutische Zusammensetzung, welche eine Verbindung nach Anspruch 1 oder ein Salz davon gemeinsam mit einem nichtgiftigen pharmazeutisch zulässigen Verdünnungs- oder Trägermittel enthält.
17. Verbindung der Formel IVa, IVb oder IVc

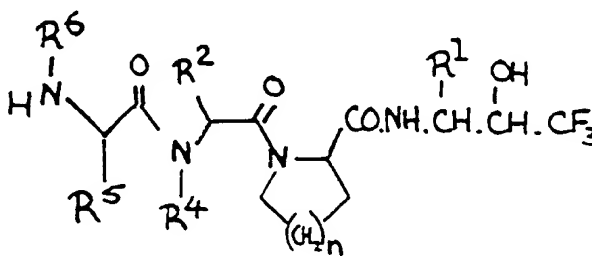
IVa



IVb



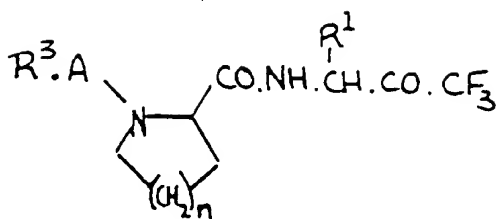
IVc



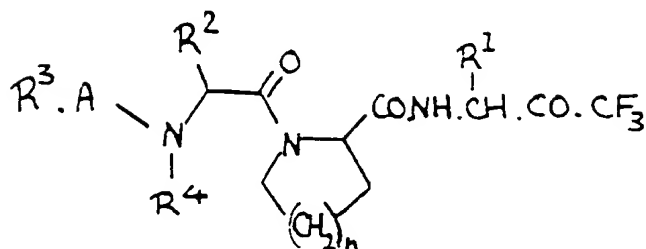
worin R^1 , R^2 , R^4 , R^5 , R^6 und n die in Anspruch 1 angegebenen Bedeutungen besitzen.

Patentansprüche für folgenden Vertragsstaat : AT

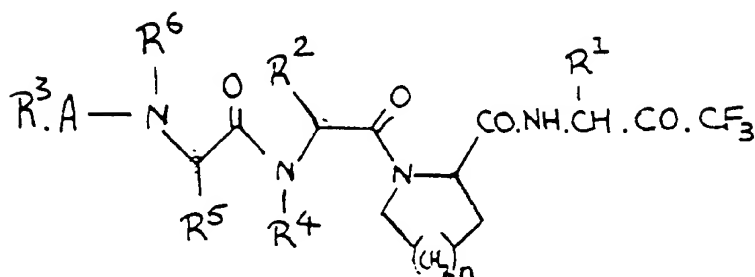
1. Verfahren zur Herstellung einer Verbindung der Formel Ia, Ib oder Ic



Ia



Ib



Ic

worin

R¹ für eine Alkyl-Gruppe mit 1 bis 5 Kohlenstoffatomen und vorzugsweise 2 bis 5 Kohlenstoffatomen steht;

R² und R⁵ jeweils unabhängig ausgewählt sind aus:

- (I) einer Alkyl-Gruppe mit 1 bis 10 Kohlenstoffatomen;
 (II) einer Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, die durch mindestens ein Mitglied aus der folgenden Gruppe substituiert ist:

- (a) Hydroxy;
 (b) Amino;
 (c) Alkylamino mit 1 bis 6 Kohlenstoffatomen;
 (d) Dialkylamino, worin jede Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 (e) Alkanoyl mit 1 bis 6 Kohlenstoffatomen;
 (f) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;
 (g) Aralkanoyl mit 8 bis 13 Kohlenstoffatomen;
 (h) Amido, welches an die Alkyl-Gruppe über entweder ein Stickstoffatom oder ein Kohlenstoffatom von diesem Amido gebunden sein kann;
 (i) Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 (j) Alkylaminocarbonyl, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
 (k) Arylcarbonylamino, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
 (l) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (m) Arylaminocarbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
 (n) Aralkylaminocarbonyl, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (o) Carboxy;
 (p) Aryloxycarbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
 (q) Aralkoxycarbonyl, worin die Aralkoxy-Gruppe 7 bis 13 Kohlenstoffatome enthält;
 (r) Alkanoyloxy mit 1 bis 6 Kohlenstoffatomen;
 (s) Aroyloxy, worin der Aryl-Teil 6, 10 oder 12 Kohlenstoffatome enthält;

- (t) Aralkanoyloxy mit 8 bis 14 Kohlenstoffatomen;
- (u) Alkylsulfonamido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (v) Aralkylsulfonamido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;
- (w) Arylsulfonamido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- 5 (x) Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl), einschließlich Acylsulfonamido, worin die Acyl-Gruppe 1 bis 7 Kohlenstoffatome enthält, wenn sie den Endteil des Acylsulfonamids bildet, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;
- 10 (y) Alkoxy-carbonyl, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (z) Aralkoxy-carbonyl-amino, worin die Aralkoxy-Gruppe 8 bis 13 Kohlenstoffatome enthält, (z.B. Benzyloxy-carbonyl-amino);
- (aa) Aryloxy-carbonyl-amino, worin die Aryloxy-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- (bb) Alkoxy-carbonyl-amino, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- 15 (cc) Aryl mit 6, 10 oder 12 Kohlenstoffatomen (z.B. Phenyl, Biphenyl, Naphthyl);
- (dd) Aryl mit 6, 10 oder 12 Kohlenstoffatomen und substituiert durch 1 bis 3 Mitglieder aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Trifluoromethyl, Hydroxy, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy-carbonyl (1 bis 6 Kohlenstoffatome), Carboxy, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome), und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;
- 20 (ee) Cycloalkyl mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl);
- (ff) Alkylureido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- 25 (gg) Aralkylureido, worin die Aralkyl-Gruppe 8 bis 13 Kohlenstoffatome enthält;
- (hh) Arylureido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält; und
- (III) einer Aryl-Gruppe mit 6 Kohlenstoffatomen, z.B. Phenyl;
- R³ ausgewählt ist aus
- (I) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen;
- 30 (II) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen und 1 bis 4 Heteroatomen, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff;
- (III) einer Alkyl-Gruppe mit 1 bis 12 Kohlenstoffatomen und gegebenenfalls 1 bis 4 Heteroatomen, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff, die an mindestens einem Kohlenstoffatom oder Stickstoffatom durch 1 bis 3 unabhängig aus der folgenden Gruppe ausgewählte Mitglieder substituiert ist:
- 35 Für Kohlenstoff:
- (a) Hydroxy, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A gebunden ist;
- (b) Amino, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A gebunden ist;
- 40 (c) Alkylamino mit 1 bis 6 Kohlenstoffatomen, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A gebunden ist;
- (d) Dialkylamino, worin jede Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, mit der Maßgabe, daß es nicht an einem Kohlenstoffatom vorliegt, das direkt an A gebunden ist;
- 45 (e) Alkanoyl mit 1 bis 6 Kohlenstoffatomen;
- (f) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;
- (g) Aralkanoyl mit 8 bis 13 Kohlenstoffatomen;
- (h) Amido, welches an die Alkyl-Gruppe über entweder ein Stickstoffatom oder ein Kohlenstoffatom von diesem Amido gebunden sein kann,
- 50 (i) Alkylcarbonyl-amino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (j) Alkylaminocarbonyl, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;
- (k) Arylcarbonyl-amino, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;
- (k)-(1) Arylcarbonyl-amino, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Carboxy, Alkoxy-carbonyl, worin das Alkoxy 1 bis 3 Kohlenstoffatome enthält, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) mit 1 bis 15 Kohlenstoffatomen substituiert ist, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;
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- (l) Arylkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(ll)-(1) Aralkylcarbonylamino, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Carboxy, Alkoxy, Carbonyl, worin das Alkoxy 1 bis 3 Kohlenstoffatome enthält, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) mit 1 bis 15 Kohlenstoffatomen substituiert ist, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(m) Arylaminocarbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(n) Aralkylaminocarbonyl, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(o) Carboxy;

(p) Aryloxy, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(q) Aralkoxy, worin die Aralkoxy-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(r) Alkanoyloxy mit 1 bis 6 Kohlenstoffatomen;

(s) Aryloxy, worin der Aryl-Teil 6, 10 oder 12 Kohlenstoffatome enthält;

(t) Alkanoyloxy mit 8 bis 13 Kohlenstoffatomen;

(u) Alkylsulfonamido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(u)-(1) Cycloalkylsulfonamido, worin der Cycloalkyl-Teil 3 bis 15 Kohlenstoffatome enthält, (z.B. Cyclohexyl, Adamantyl, Norbornyl);

(v) Aralkylsulfonamido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(w) Arylsulfonamido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(x) Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome), einschließlich Acylsulfonamido, worin die Acyl-Gruppe 1 bis 7 Kohlenstoffatome enthält, wenn sie den Endteil des Acylsulfonamids bildet, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(y) Alkoxy, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(z) Aralkoxy, worin die Aralkoxy-Gruppe 8 bis 13 Kohlenstoffatome enthält, (z.B. Benzyloxy, t-Butyloxy);

(z)-(1) Arylaminocarbonyloxy, worin die Aryl-Gruppe 8 bis 13 Kohlenstoffatome enthält;

(z)-(2) Aryloxy, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;

(z)-(3) Aryloxy, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält und durch ein Mitglied aus der Gruppe Aminocarbonyl, Aminocarbonylalkyl, worin das Alkyl 1 bis 3 Kohlenstoffatome enthält, Alkoxy, Carbonyl mit 1 bis 3 Kohlenstoffatome und Carboxy substituiert ist;

(aa) Aryloxy, worin die Aryloxy-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(aa)-(1) Arylaminocarbonyloxy, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(bb) Alkoxy, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(bb)-(1) Alkoxy, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält und gegebenenfalls mit einem Kohlenstoffatom an ein Kohlenstoffatom einer aromatischen heterocyclischen Gruppe gebunden ist, wie sie in (gg) unter R³ beschrieben ist;

(bb)-(2) Alkoxy, worin die Alkoxy-Gruppe 1 bis 6 Kohlenstoffatome enthält und durch eine aliphatische heterocyclische Gruppe substituiert ist, wie sie in (ff) unter R³ beschrieben ist;

(bb)-(3) Aryloxy, worin das Aryl 6 oder 10 Kohlenstoffatome und das Alkyl 1 bis 6 Kohlenstoffatome enthält;

(bb)-(4) Alkylaminocarbonyloxy, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(cc) Aryl mit 6, 10 oder 12 Kohlenstoffatomen (z.B. Phenyl, Naphthyl, Biphenyl);

(cc)-(1) Aryloxy mit 6, 10 oder 12 Kohlenstoffatomen;

(dd) Aryl mit 6, 10 oder 12 Kohlenstoffatomen und substituiert durch 1 bis 3 Mitglieder, die unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy, Carbonyl (2 bis 6 Kohlenstoffatome), Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome) ausgewählt sind, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(dd)-(1) Aryloxy mit 6, 10 oder 12 Kohlenstoffatomen und substituiert an Kohlenstoff durch 1 bis 3 Mitglieder, die unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy, Carbonyl (2 bis 6 Kohlenstoffatome), Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome) ausgewählt sind, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

Kohlenstoffatome), Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo, Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome) ausgewählt sind, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

(ee) Cycloalkyl mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl);

(ee)-(1) Cycloalkyloxy mit 3 bis 15 Kohlenstoffatomen;

(ff) eine aliphatische heterocyclische Gruppe mit mindestens 4 Atomen, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff, (z.B. Morpholin, Piperazin), worin die aliphatische heterocyclische Gruppe gegebenenfalls 1 oder 2 Doppelbindungen enthalten kann, welche aliphatische heterocyclische Gruppe an irgendeinem Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkanoyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Aryloxycarbonyl-Gruppe, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält, eine Aralkyloxycarbonyl-Gruppe, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält, oder eine Alkoxy-carbonyl-Gruppe, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, substituiert sein kann;

(ff)-(1) eine aliphatische heterocyclische Oxy-Gruppe, worin die Oxy-Gruppierung direkt an ein Kohlenstoffatom der aliphatischen heterocyclischen Gruppe mit mindestens 5 Atomen gebunden ist, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig ausgewählt ist aus Stickstoff und Sauerstoff, (z.B. Morpholin, Piperazin), worin die aliphatische heterocyclische Gruppe gegebenenfalls 1 oder 2 Doppelbindungen enthalten kann, welche aliphatische heterocyclische Gruppe an irgendeinem Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkanoyl-Gruppe mit 1 bis 6 Kohlenstoffatomen, eine Aryloxycarbonyl-Gruppe, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält, eine Aralkyloxycarbonyl-Gruppe, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält, oder eine Alkoxy-carbonyl-Gruppe, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, substituiert sein kann;

(gg) eine aromatische heterocyclische Gruppe, die folgendes enthält: (1) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig ausgewählt ist aus Schwefel, Stickstoff und Sauerstoff, und (2) 1 bis 3 fünf- oder sechsgliedrige Ringe, von denen mindestens einer aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen, Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome) und Aminocarbonyl substituiert sein können, und mit der weiteren Maßgabe, daß jedes Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann;

(gg)-(1) eine aromatische heterocyclische Oxy-Gruppe, worin die Oxy-Gruppierung direkt an ein Kohlenstoffatom einer aromatischen heterocyclischen Gruppe gebunden ist, die folgendes enthält: (1) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig ausgewählt ist aus Schwefel, Stickstoff und Sauerstoff, und (2) 1 bis 3 fünf- oder sechsgliedrige Ringe, von denen mindestens einer aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen, Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome) und Aminocarbonyl substituiert sein können, und mit der weiteren Maßgabe, daß jedes Stickstoffatom durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann;

(hh) Alkylureido, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält;

(hh)-(1) Cycloalkylureido, worin die Alkyl-Gruppe 3 bis 15 Kohlenstoffatome enthält;

(ii) Aralkylureido, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält;

(jj) Arylureido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält;

(jj)-(1) Arylureido, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält und durch 1 bis 3 Mitglieder substituiert ist, die unabhängig ausgewählt sind aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy-carbonyl (2 bis 6 Kohlenstoffatome), Carboxy, Aminocarbonylalkyl (2 bis 6 Kohlenstoffatome), Aminocarbonyl, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylaminocarbonyl) (1 bis 15 Kohlenstoffatome), einschließlich Acylsulfonamido, worin die Acyl-Gruppe 1 bis 7 Kohlenstoffatome enthält, wenn sie den Endteil des Acylsulfonamids bildet, und

mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;

Für Stickstoff:

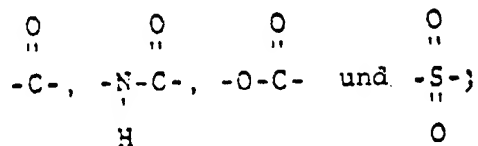
- (a) Alkyl mit 1 bis 3 Kohlenstoffatomen;
- (b) Alkanoyl mit 2 bis 6 Kohlenstoffatomen;
- (c) Arylcarbonyl, worin das Aryl 6, 10 oder 12 Kohlenstoffatome enthält;
- (d) Aralkanoyl mit 8 bis 14 Kohlenstoffatomen;
- (e) Formyl;
- (f) eine aliphatische heterocyclische Gruppe, worin die Amino-Gruppierung direkt an ein Kohlenstoffatom einer aliphatischen heterocyclischen Gruppe gebunden ist, die in (ff) für die Kohlenstoff-Substituenten definiert ist;
- (g) eine aromatische heterocyclische Gruppe, worin die Amino-Gruppierung direkt an ein Kohlenstoffatom der aromatischen heterocyclischen Gruppe gebunden ist, die in (gg) für die Kohlenstoff-Substituenten definiert ist;
- (IV) einer Aryl-Gruppe mit 6, 10 oder 12 Kohlenstoffen;
- (V) einer Aryl-Gruppe mit 6, 10 oder 12 Kohlenstoffatomen, die in geeigneter Weise durch 1 bis 3 Mitglieder substituiert ist, die unabhängig ausgewählt sind aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Hydroxy, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkoxycarbonyl mit 2 bis 6 Kohlenstoffatomen, Carboxy, Alkylcarbonylamino, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylamino-carbonyl) mit 1 bis 15 Kohlenstoffatomen, und mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann;
- (VI) einer Cycloalkyl-Gruppe mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl);
- (VI)-(1) einer Cycloalkyl-Gruppe mit 3 bis 15 Kohlenstoffatomen (z.B. Cyclohexyl, Adamantyl, Norbornyl), die durch ein Mitglied aus der Gruppe Carboxy und Alkoxy-carbonyl, worin die Alkoxy-Gruppe 1 bis 4 Kohlenstoffatome enthält, substituiert ist;
- (VII) einer aliphatischen heterocyclischen Gruppe mit mindestens 5 Atomen, die 1 bis 5 Kohlenstoffatome und 1 bis 4 Heteroatome enthält, von denen jedes unabhängig aus Stickstoff und Sauerstoff ausgewählt ist, (z.B. Morpholin, Piperazin), welche an irgendeinem Stickstoffatom durch ein Mitglied aus der Gruppe Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 1 bis 6 Kohlenstoffatomen, Aryloxy-carbonyl, worin die Aryl-Gruppe 6, 10 oder 12 Kohlenstoffatome enthält, Aralkoxy-carbonyl, worin die Aralkyl-Gruppe 7 bis 13 Kohlenstoffatome enthält, und Alkoxy-carbonyl mit 2 bis 7 Kohlenstoffatomen substituiert sein kann, mit der Maßgabe, daß, wenn A für OCO oder NHCO steht, das A an ein Kohlenstoffatom der aliphatischen heterocyclischen Gruppe gebunden sein muß;
- (VIII) einer aromatischen heterocyclischen Gruppe, die folgendes enthält: (a) 1 bis 15 Kohlenstoffatome und 1 bis 4 Heteroatome, von denen jedes unabhängig aus Schwefel, Stickstoff und Sauerstoff ausgewählt ist, und (b) 1 bis 3 fünf- oder sechsgliedrige Ringe, von denen mindestens einer aromatisch ist, wobei gegebenenfalls bis zu 3 Kohlenstoffatome des aromatischen Rings oder der aromatischen Ringe an irgendeinem Kohlenstoffatom durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo, Trifluoromethyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen und Carboxy substituiert sein können, und mit der weiteren Maßgabe, daß jeder Stickstoff durch eine Alkyl-Gruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann, und daß, wenn A für OCO oder NHCO steht, das A an ein Kohlenstoffatom der aromatischen heterocyclischen Gruppe gebunden sein muß;
- (IX) einer Alkenyl-Gruppe mit 2 bis 10 Kohlenstoffatomen und mit mindestens einer Doppelbindung; und
- (X) einer Alkenyl-Gruppe mit 2 bis 10 Kohlenstoffatomen und mit mindestens einer Doppelbindung, die durch ein aus der folgenden Gruppe ausgewähltes Mitglied substituiert ist:
 - (a) Aryl mit 6 oder 10 Kohlenstoffatomen;
 - (b) Aryl mit 6 oder 10 Kohlenstoffatomen, das durch 1 bis 3 Mitglieder substituiert ist, die unabhängig aus der Gruppe Chloro, Bromo, Jodo, Fluoro, Hydroxy, Trifluoromethyl, Alkyl (1 bis 6 Kohlenstoffatome), Alkoxy (1 bis 6 Kohlenstoffatome), Alkoxy-carbonyl (2 bis 6 Kohlenstoffatome), Carboxy, 5-Tetrazolo und Acylsulfonamido (nämlich Acylaminosulfonyl und Sulfonylamino-carbonyl) (1 bis 15 Kohlenstoffatome) ausgewählt sind, (1 mit der Maßgabe, daß, wenn das Acylsulfonamido ein Aryl enthält, das Aryl weiter durch ein Mitglied aus der Gruppe Fluoro, Chloro, Bromo, Jodo und Nitro substituiert sein kann; und

(c) Ureidocarbonyl;

R⁴ und R⁵ unabhängig ausgewählt sind aus Wasserstoff oder Methyl;

n für 0, 1 oder 2 steht; und

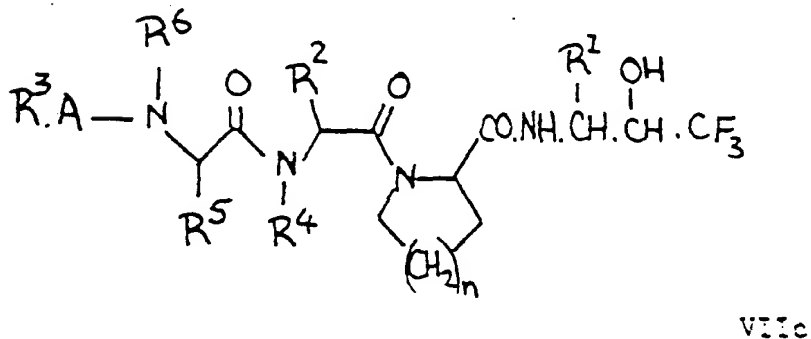
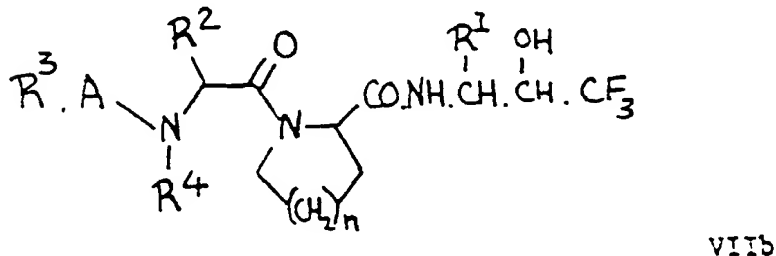
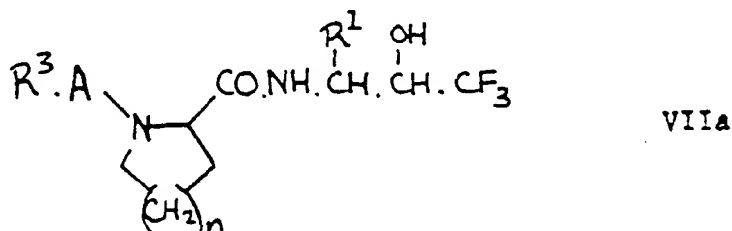
A ausgewählt ist aus



oder, sofern geeignet, eines Säure- oder Basenadditionssalzes davon; mit der Maßgabe, daß,

1. Alkyle gerade oder verzweigt sein können;
2. kein Kohlenstoffatom eines Alkyls direkt an zwei Heteroatome gebunden sein kann;
3. kein Heteroatom direkt an Schwefel, Stickstoff oder Sauerstoff gebunden sein; und
4. Alkenyle von (IX) und (X) für R³ nicht 1,1-disubstituiert sein können und ein Kohlenstoff einer Doppelbindung nicht direkt an Sauerstoff oder Stickstoff gebunden sein kann,

bei welchem Verfahren eine Verfahren der Formel VIIa, VIIb bzw. VIIc



oxidiert wird.

2. Verfahren nach Anspruch 1, bei welchem die Oxidation unter Verwendung eines der folgenden Mittel ausgeführt wird:
 - (a) Oxalylchlorid, Dimethylsulfoxid und tertiäres Amin in Methylenchlorid;
 - (b) Essigsäureanhydrid und Dimethylsulfoxid;
 - 5 (c) Chromtrioxid/Pyridin-Komplex in Methylenchlorid; und
 - (d) Dess-Martin-Perjodinan in Methylenchlorid.
3. Verfahren nach Anspruch 1 oder 2, bei welchem die Oxidation unter Verwendung von Dess-Martin-Perjodinan in Methylenchlorid ausgeführt wird.
- 10 4. Verfahren nach Anspruch 1, bei welchem eine zweite Verbindung der Formel Ia, Ib oder Oc, die eine Carboxy-Gruppe in R², R³ oder R⁵ enthält, aus der genannten ersten Verbindung der Formel Ia, Ib bzw. Ic hergestellt wird, wobei die erste Verbindung eine Carbonsäureester-Gruppe in R², R³ oder R⁵ enthält und bei welchem Verfahren die Carbonsäureester-Gruppe in die entsprechende Carboxy-Gruppe
15 umgewandelt wird.
5. Verfahren nach Anspruch 4, bei welchem die genannte Carbonsäureester-Gruppe durch Hydrolyse in die entsprechende Carboxy-Gruppe überführt wird.
- 20 6. Verfahren nach Anspruch 1 oder 4, bei welchem eine dritte Verbindung der Formel Ia, Ib oder Ic, die eine Sulfonylaminocarbonyl-Gruppe in R², R³ oder R⁵ enthält, aus der ersten oder zweiten Verbindung der Formel Ia, Ib bzw. Ic, wobei die erste oder zweite Verbindung eine Carboxy-Gruppe in R², R³ oder R⁵ enthält, durch Kuppeln dieser Carboxy-Gruppe mit der Amino-Gruppe eines Sulfonamids hergestellt wird.
- 25 7. Verfahren nach Anspruch 6, bei welchem das Kupplungs-Verfahren mit einem der folgenden Mittel ausgeführt wird:
 - (a) 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimidhydrochlorid und 4-Dimethylaminopyridin in Methylenchlorid; und
 - 30 (b) 1,3-Dicyclohexylcarbodiimid und 4-Dimethylaminopyridin in Methylenchlorid.

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